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Proposed Re-evaluation Decision

Metsulfuron methyl

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Overview

Proposed Re-evaluation Decision for Metsulfuron methyl

After a re-evaluation of the herbicide metsulfuron methyl, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration for the sale and use of products containing metsulfuron methyl in Canada.

An evaluation of available scientific information found that products containing metsulfuron methyl have value in the food and crop industry and do not present unacceptable risks to human health or the environment. As a condition of the continued registration of metsulfuron methyl use on terrestrial food and feed crops and non-crop areas in the Prairie provinces and British Columbia, new risk-reduction measures are proposed for inclusion on the labels of all metsulfuron methyl products. No additional data are being requested at this time.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing metsulfuron methyl registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address the new risk-reduction measures.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for metsulfuron methyl and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of metsulfuron methyl.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

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[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration[2]. The Act also requires that products have value[3] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous hazard and risk assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in both humans (e.g. children) and organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

Before making a re-evaluation decision on metsulfuron methyl, the PMRA will consider all comments received from the public in response to this consultation document[4]. The PMRA will then publish a Re-evaluation Decision document[5] on metsulfuron methyl, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this overview, please refer to the Science Evaluation section of this consultation document.

What Is Metsulfuron methyl?

Metsulfuron methyl is a selective systemic residual sulfonylurea herbicide. It is registered for postemergent use on terrestrial food and feed crops and non-crop areas in the Prairie provinces and British Columbia. Metsulfuron methyl may be used to control a broad spectrum of annual and perennial broadleaf weeds as well as some undesirable brush or woody plants. Metsulfuron methyl is applied once per year at a rate of 4.5 to 90.0 g a.i./ha by ground equipment only. Metsulfuron methyl residue in soil can persist for a long

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

period, potentially limiting recropping options. For use on wheat, barley and established creeping red fescue, metsulfuron methyl is restricted to use on soil of pH 7.9 or lower.

Health Considerations

Can Approved Uses of Metsulfuron Methyl Affect Human Health?

Metsulfuron methyl is unlikely to affect your health when used according to the revised label directions.

People could be exposed to metsulfuron methyl by consuming food and water, handling treated crops, working as a mixer/loader/handler, or by entering treated sites. The PMRA considers two key factors when assessing health risks: the dose levels where no health effects occur and the dose levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when using metsulfuron methyl products according to label directions.

An acute overexposure to metsulfuron methyl can produce a variety of symptoms in animals and humans. Symptoms may include weight loss, nasal secretions, and stained perineal areas. Contact with the eye may cause corneal opacity, moderate inflammation of the iris and moderate to severe conjunctivitis.

Additional toxic effects include diarrhea, reduced serum protein and increased relative organ weights. Effects noted at high doses in pregnant females include increased mortality, red or orange coloured urine, decreased motor activity and impaired righting reflex. However, these effects would not occur when metsulfuron methyl products are used according to label directions. Based on the weight of evidence, metsulfuron methyl is considered non-carcinogenic. A cancer risk assessment was not required.

Although there are no risks of concern based on current uses of metsulfuron methyl, protective measures (protective personal equipment and improved work practices) have been proposed to update the product labels to the current standard and to further reduce the level of human exposure to metsulfuron methyl.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to metsulfuron methyl was estimated from residues in treated crops and drinking water, including the most highly exposed subpopulation (e.g. children one to six years old). This aggregate exposure (i.e. to metsulfuron methyl from food and drinking water) represents less than 5% of the chronic reference dose.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs for metsulfuron methyl are currently specified for kidney, fat, meat and meat byproduct of cattle, goat and hog as well as for milk. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. The proposed amendments to the default MRL for metsulfuron methyl can be found in the Science Evaluation section 8.1.2 of this consultation document.

Risks in Residential and Other Non-Occupational Environments

Residential and other non-occupational risks are not of concern.

Metsulfuron methyl is not registered for use in any residential areas. Therefore, there are no potential residential or other non-occupational risks.

Occupational Risks From Handling Metsulfuron Methyl

Occupational risks are not of concern when used according to the revised label directions.

Based on both the precautions and directions for use on the original product labels reviewed for this re-evaluation, and also considering the use of appropriate protective equipment, the risk estimates associated with mixing, loading and applying activities meet current standards for all the scenarios and are not of concern. The proposed personal protection equipment are long pants, long-sleeved shirt, and chemical-resistant gloves.

Postapplication risks are not of concern when used according to the revised label directions.

Occupational postapplication risk assessments consider exposures to workers re-entering treated sites, agricultural and industrial areas. Based on the precautions and directions for use on the original product labels reviewed for this re-evaluation, and also considering proposed protective measures (revised restricted-entry interval), postapplication risk estimates to re-entry workers performing high exposure activities (scouting) meet current standards and are not of concern.

Environmental Considerations

What Happens When Metsulfuron methyl is Introduced Into the Environment?

Metsulfuron methyl poses a potential risk to terrestrial and aquatic plants, therefore, additional risk-reduction measures need to be observed.

When metsulfuron methyl is applied for control of weeds in crops, some of it finds its way into soil and water. However, the chemical is not expected to persist as it is rapidly broken down by soil microbes and by chemical reaction in water. The breakdown chemical products that are formed persist for a longer period of time. Both metsulfuron methyl and its breakdown products are mobile and hence can move freely in soil. However, field studies have not shown any evidence that these residues in the soil will contaminate groundwater. Water runoff on the soil surface can move the residues into nearby bodies of water such as ponds and rivers. Water monitoring of these bodies of water have revealed residues, but at concentrations below levels of concern.

When metsulfuron methyl is used for weed control in crops, there is a potential that sensitive plant species on land and in water may be exposed to the chemical as a result of the spray drifting or runoff. Some of these species are sensitive to the chemical and would be adversely affected. To minimize the potential exposure, strips of land (buffer zones) between the agricultural field and the nontarget terrestrial or aquatic areas will be left unsprayed. The width of these buffer zones will be specified on the product label. Metsulfuron methyl is not a concern to wild birds and mammals, bees and other arthropods or aquatic organisms like fish, amphibians and invertebrates because concentrations in the environment are not expected to be harmful.

Value Considerations

What is the Value of Metsulfuron methyl?

Metsulfuron methyl controls a wide spectrum of broadleaf weeds in wheat, barley and forage grasses at a very low application rate (4.5 g a.i./ha). It also controls some undesirable brush or woody plants in pasture, rangeland and non-crop areas at a low application rate.

Although a relatively small quantity is used, metsulfuron methyl contributes to the reduction of the economic losses caused by weeds, estimated at a total of $362.5 million in the early 1990s for wheat, barley and forage grasses. Metsulfuron methyl is the only alternative to the selective herbicides registered for use on established creeping red fescue for the control of broadleaf weeds. It is also the only alternative to the selective herbicides registered for use on pasture, rangeland and non-crop areas for the control of western snowberry, trembling aspen and other undesirable brush or woody plants. Compared to alternative herbicides, metsulfuron methyl controls late germinating weeds, has greater flexibility in application timing, provides better control of undesirable woody plants and is applied at a low rate which contributes to less chemical load in the environment. Although metsulfuron methyl plays a role in mitigating resistance development in weeds to other herbicide groups, consideration has to be given to resistance management as more weed species are reported to be resistant to herbicides that inhibit acetolactate synthase (such as metsulfuron methyl) than to herbicides having other modes of action.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. As a result of the re-evaluation of metsulfuron methyl, the PMRA is proposing further risk-reduction measures for product labels.

- **Human Health**
  - To protect mixer/loader/applicators: additional protective equipment
  - To protect workers re-entering treated sites: a restricted-entry interval
  - To protect workers using wettable granular formulation: additional precautionary statements and directions for use
  - To avoid drift to areas of human habitation or areas of human activity: precautionary statements

- **Environment**
  - To protect non-target terrestrial and aquatic plants: adding precautionary statements and directions for use, as well as buffer zones for terrestrial and aquatic plants
  - To reduce the potential runoff of metsulfuron methyl to adjacent aquatic habitats: statements cautioning use on sites with characteristics that may enhance runoff when heavy rain is forecasted

Next Steps

Before making a re-evaluation decision on metsulfuron methyl, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision document, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

When the re-evaluation decision is made, the PMRA will publish an Evaluation Report on Metsulfuron methyl in the context of this re-evaluation decision (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

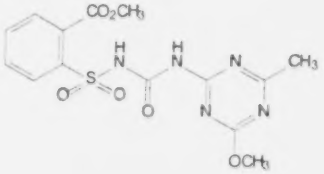
1.0 Introduction

Metsulfuron methyl is a selective systemic residual herbicide. It belongs to the sulfonylurea chemical family and is classified as a Group 2 herbicide. The herbicidal activity of metsulfuron methyl is due to the inhibition of the plant enzyme acetolactate synthase (ALS), also called acetohydroxyacid synthase (AHAS).

Following the re-evaluation announcement for metsulfuron methyl, E.I. du Pont Canada Company, the registrant of the technical grade active ingredient (TGAI) and primary data provider in Canada, indicated it would continue to support all uses included on the label of Commercial Class end-use products. There are no Domestic Class products containing metsulfuron methyl registered in Canada.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Metsulfuron methyl
Function	Herbicide
Chemical family	Sulfonylurea
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Methyl 2-[[3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)ureido]sulfonyl]benzoate
2. Chemical Abstracts Service (CAS)	Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]- carbonyl]amino]sulfonyl]benzoate
CAS Registry Number	74223-64-6
Molecular formula	$C_{14}H_{15}N_5O_6S$
Molecular weight	381.4
Structural formula	

Basic manufacturers	DuPont Agricultural Caribe Ind. Highway 686, Km 2.3 Manati, Puerto Rico	DuPont Agricultural Chemicals Ltd. Shanghai (DUPAC) P.R. China
Purity of the technical grade active ingredient	97.7% NS (limits: 96.0 - 100%)	
Registration number	20213	

Identity of impurities of human health or environmental concern:

Based on the manufacturing process, the product is not expected to contain impurities of human health or environmental concern as identified in Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, Section 2.13.4 or Toxic Substances Management Policy (TSMP) Track 1 substances as identified in Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, Appendix II.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Henry's law constant	2.3×10^{-10} Pa m^3 mol^{-1}
Vapour pressure	3.3×10^{-7} mPa
Ultraviolet–visible spectrum	pH / λ_{max} 3 225 5 233 7 233 9 233
Solubility in water at 25	pH / Solubility (g/L) 5 0.55 7 2.79 9 213
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = -1.74 (pH 7)
Dissociation constant (pKa)	pKa = 3.3

2.3 Description of Registered Metsulfuron methyl Uses

Appendix I lists all metsulfuron methyl products registered under the authority of the *Pest Control Products Act*, specifically including one technical grade active ingredient, one manufacturing concentrate and five Commercial Class end-use products.

Appendix II lists all the uses for which metsulfuron methyl is presently registered. All uses are supported by the registrant at the time of initiation of re-evaluation and were, therefore, considered in the health and environmental risk assessments. Also presented is whether any of the uses were added through the PMRA Minor Use Program. While currently supported by the registrant, the data supporting these minor uses was originally generated by a user group.

Uses of metsulfuron methyl belong to the following Use-site categories: terrestrial food crops, terrestrial feed crops and industrial and domestic vegetation control for non-food sites. The sites include wheat (spring and durum), barley, forage grasses (established creeping red fescue, orchard grass, crested and intermediate wheat grass), pasture, rangeland and non-crop areas (utility rights of way, roadsides, industrial sites, and fencelines).

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. The health effects noted here were observed in animals at dose levels at least 100-fold (often much higher) above levels to which humans are normally exposed through use of products containing this chemical.

3.1 Toxicological Summary

The toxicology database supporting metsulfuron methyl is primarily based on studies from the technical registrant. In laboratory animals, metsulfuron methyl is of low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is non-irritating to rabbit skin, severely irritating to rabbit eyes, and a non-sensitizer in Guinea pigs. Signs of acute toxicity induced by metsulfuron methyl are weight loss, stained and wet perineal areas, and nasal discharge.

With oral exposure, metsulfuron methyl was rapidly absorbed from the gastrointestinal tract and accumulation within tissues was minimal. Within 72 to 96 hours, 71 to 95% of the administered dose was recovered from the urine, and 5 to 13% from the feces. The parent compound accounted for most of the urinary (77–90%) and fecal (1.8–6.2%) activity. The major metabolic pathway was the cleavage of the sulfonylurea bridge and subsequent demethylation.

In a 21-day dermal study in rabbits there was an increase in diarrhea at the two highest doses. Dermal effects in this study included slight to severe erythema and slight to moderate edema at the highest dose and diffuse/multifocal dermatitis at the two highest doses.

In short- and long-term feeding studies, the major effect was a slight reduction in body weight or body weight gain. In the 90-day rat study, there were also reductions in relative liver weight and serum protein. No adverse effects were noted in a sub-chronic (90-day) mouse study or in a three-month/1 year dog study.

No treatment-related effects were noted in the mouse oncogenicity study. In the chronic rat study, in addition to a reduction in body weight, body weight gain and food consumption, relative kidney, brain and heart weights were increased. A slightly increased incidence of hepatocellular adenomas in males and an increased incidence of C-cell adenomas of the thyroid in females were both within historical control levels and therefore are not considered treatment-related. All genotoxicity studies were negative with the exception of an in vitro chromosome aberration assay (CHO cells) which was positive only at a high dose level (>1000 mg/l). Metsulfuron methyl is considered non-carcinogenic.

In a developmental toxicity study in the rat, dams showed a reduction in food consumption during the treatment period (with a post-treatment increase) and an increase in clinical signs, including vocalization to touch, ungroomed coat, excess salivation, "tip-toe" walking, and urine-stained abdominal fur. There were no treatment-related developmental effects. In rabbits, maternal effects included increased mortality, reduction in body weight gains and clinical signs of toxicity such as decreased motor activity, impaired righting reflex, and red or orange-coloured urine. There were no developmental effects.

In a 2-generation reproductive study in the rat, reduction in parental body weight and body weight gain was observed at the highest dose in both generations during premating only. No treatment-related effects on offspring or reproduction were noted.

Reference doses have been set based on the NOAEL for the most sensitive indicators of toxicity, namely decreases in body weight, body weight gain and food consumption, and increases in relative kidney, brain and heart weights, in rats. Reference doses incorporate uncertainty factors to account for extrapolating between laboratory animals and humans, and to provide a margin of safety for the severe effect of maternal deaths noted in the rabbit developmental study.

The toxicology profile of metsulfuron methyl and toxicology endpoints used in the risk assessment of metsulfuron methyl are summarized in Appendix III and IV.

3.2 Occupational and Residential Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating safety factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require mitigation measures to reduce risk.

3.2.1 Toxicological Endpoints

To estimate the risk to the general population from short- and intermediate-term dermal exposure, a NOAEL of 125 mg/kg bw/day from 21-day dermal study in the rabbit was used. The NOAEL was based on increased diarrhea at a LOAEL of 500 mg/kg bw/day. A target MOE of 100 is based on the standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability.

To estimate the risk to females 13+, from short- and intermediate-term dermal exposure, a NOAEL of 100 mg/kg bw/day from a developmental study in the rabbit was used. The NOAEL was based on increased mortality, decreased body weight gain, decreased motor activity, impaired righting reflex, and orange/red-coloured urine at a LOAEL of 300 mg/kg bw/day. A target MOE of 1000 is based on the standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability, with an extra factor of 10 for severity of effect.

To estimate the risk to the general population from short- and intermediate-term inhalation exposure, an oral NOAEL of 84 mg/kg bw/day from a 90-day feeding study in the rat was used. The NOAEL was based on reduced body weight and body weight gain, and reduced serum protein at a LOAEL of 659 mg/kg bw/day. A target MOE of 100 is based on the standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability.

To estimate the risk to females 13+, from short- and intermediate-term inhalation exposure, an oral NOAEL of 100 mg/kg bw/day from a developmental study in the rabbit was used. The NOAEL was based on increased mortality, decreased body weight gain, decreased motor activity, impaired righting reflex, and orange/red-coloured urine at a LOAEL of 300 mg/kg bw/day. A target MOE of 1000 is based on the standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability, with an extra factor of 10 for severity of effect.

The PMRA does not consider metsulfuron methyl to be a possible human carcinogen based on a weight-of-evidence approach.

Dermal Absorption

A NOAEL from a suitable dermal study was not available for use in the dermal risk assessment. Since the dermal risk assessment is based on a NOAEL from an oral study (see Section 3.2.1), an estimate of dermal absorption was required to refine the dermal exposure estimates. Based on the weight-of-evidence from the analysis of the physical-chemical properties, the comparison of oral and dermal toxicity, and the comparison of metsulfuron methyl physical-chemical properties with a similar compound, a 35% dermal absorption value was incorporated into the dermal estimates of exposure for all scenarios.

3.2.2 Occupational Exposure and Risk

3.2.2.1 Mixer/Loader/Applicator Exposure and Risk

Workers can be exposed to metsulfuron methyl through mixing, loading or applying the herbicide during normal use, and when re-entering a treated site to conduct activities such as scouting and/or handling treated crops.

There are potential exposures to mixers, loaders and applicators. The following supported uses were assessed:

- Mixing and loading wettable granules for application to terrestrial field crops and non-crop land;
- Mixing and loading wettable granules in water-soluble packaging (WSP) for application to terrestrial field crops and non-crop land;
- Applying wettable granules as sprays to terrestrial field crops and non-crop land by groundboom or right-of-way sprayer.
- Mixing, loading and applying wettable granules to non-crop land by low pressure handwand (LPHW), high pressure handwand (HPHW) or backpack.
- Mixing, loading and applying wettable granules in WSP by LPHW, HPHW or backpack.

Occupational handlers of metsulfuron methyl include farmers and custom agricultural applicators who mix, load and apply the herbicide. As only one application is permitted per season, the duration of exposure for farmers and custom applicators is short- to intermediate-term (1 to 30 days). Exposure for all crop scenarios is predominantly dermal, with inhalation accounting for a minor component of overall exposure.

The PMRA estimated handler exposure based on the following level of personal protective equipment (PPE):

Baseline PPE: Long pants, long-sleeved shirt and chemical-resistant gloves (unless specified otherwise, i.e. for groundboom application, chemical-resistant gloves are not included in the scenario).

Mixer/loader/applicator exposure estimates are based on the best available data at this time. The assessment might be refined with product-specific exposure data, biological monitoring data, or dermal absorption data.

No chemical specific exposure studies were available for use in the re-evaluation of metsulfuron methyl. Thus, appropriate dermal and inhalation exposures were estimated using the *Pesticide Handlers Exposure Database (PHED), Version 1.1*. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment.

In some cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing additional PPE and/or using engineering controls. Surrogate data for wettable granules in WSP were not available in PHED, therefore closed mixing and loading data for wettable granules were used.

For some scenarios (e.g. hand-held equipment), estimating exposure from mixing, loading and applying wettable granules in WSP was not possible using PHED. In these situations, exposure units from mix/load/apply with open pour liquid for low pressure handwand and backpack were used.

Similarly, the PHED did not contain data to estimate exposure from mixing, loading and applying wettable granules by hand-held equipment. For LPHW, the available PHED values from mixing, loading and applying a wettable powder by LPHW was used as surrogate. However, this scenario is not available in PHED for HPHW and backpack. Therefore, the unit exposure numbers were estimated by using the following formula: [Exposure from mixing, loading and applying a liquid with HPHW or backpack] + [Exposure from mixing and loading wettable granules].

PHED unit exposures coupled with information on the amount of metsulfuron methyl handled per day was used to estimate handler exposure. The amount handled per day is based upon the maximum label application rate and default assumptions on the area (of crop) which can reasonably be treated in one day.

Calculated MOEs exceed the target MOE for all exposure scenarios and are summarized in Appendix V, Table 1.

3.2.2.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers entering treated agricultural sites to conduct activities involving foliar contact. Based on the metsulfuron methyl use pattern, there is potential for short-term (1 to 30 days) postapplication exposure to metsulfuron methyl residues for workers.

Chemical-specific dislodgeable foliar residue (DFR) data and activity specific transfer coefficients (TC) were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application. DFR data include the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. A TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination (e.g. hand harvesting apples, scouting late season cotton) and reflect standard agricultural work clothing worn by adult workers. Postapplication exposure activities include scouting, irrigation, mechanical weeding and mowing.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely re-enter. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE (i.e. > 1000 for short-term exposure scenarios).

Although metsulfuron methyl is applied to agricultural and industrial areas including terrestrial feed and food crops, as well as non-crop land, no relevant DFR studies were available. As a result, a conservative default value of 20% of the application rate with a 10% dissipation per day was used.

The postapplication risk estimates include a number of conservative inputs, such as the assumption that workers are exposed to residues following the maximum number of applications (only one in this case) at the maximum rate.

Calculated MOEs exceed the target MOE on day 0, and proposed REIs are set at 12 hours. Postapplication exposure calculations for each use site are summarized in Appendix V, Table 2 .

3.2.3 Residential Exposure and Risk Assessment

3.2.3.1 Residential Handler and Risk

No domestic class products containing metsulfuron methyl are registered in Canada; therefore, a residential handler assessment was not required.

3.2.3.2 Bystander Exposure and Risk

For bystanders, exposure is expected to be much less than that of field workers and is considered negligible.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to metsulfuron methyl from potentially treated imports is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life. For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when risk exceeds 100% of the reference dose. PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessments procedures.

Residue estimates used in the dietary risk assessment (DRA) may be conservatively based on the maximum residue limits (MRL) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (PDP).

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.03), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendix VI and VII.

3.3.1 Determination of Acute Reference Dose

An acute (1 day) reference dose (ARfD) was not calculated since there was not an acute endpoint of concern.

3.3.2 Determination of Acceptable Daily Intake

The acceptable daily intake (ADI) is the dose that an individual can be exposed to over the course of a lifetime and expect no adverse health effects. The ADI selected for metsulfuron methyl was based on a NOAEL of 25 mg/kg bw/day from a 2-year feeding study in rats. The endpoint selected was based on decreased body weight, body weight gain and food consumption, and increased relative kidney, brain and heart weights at a LOAEL of 250 mg/kg bw/day. An overall uncertainty factor of 300 was required to account for interspecies extrapolation (10-fold), intraspecies variability (10-fold) and severity of effect (3-fold) resulting in an ADI of 0.0833 mg/kg bw/day (25 mg/kg bw/day ÷ 300). The additional 3× safety factor for severity of effect provides a margin of safety of at least 1000 to the NOAEL (100 mg/kg bw/day) for maternal death noted in the rabbit developmental study. Since the chronic rat NOAEL of 25 mg/kg bw/day is partially protective for the maternal death, a full 10× for severity of effect is not required. The ADI is considered to be protective of all populations, including infants and children, and females of childbearing age (13–49 years).

3.3.3 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary exposure is acceptable.

The chronic potential daily intake accounted for less than 5% of the ADI for all subpopulations and is, therefore, not of concern.

3.3.4 Cancer Potency Factor

A cancer risk assessment was not conducted since the metsulfuron methyl database did not suggest any carcinogenic potential in mice or rats.

3.4 Exposure From Drinking Water

3.4.1 Concentrations in Drinking Water

Metsulfuron methyl residues in potential drinking water sources were estimated using computer simulation models. The estimated drinking water concentration value used in the exposure model is 1 part per billion (ppb).

3.4.2 Drinking Water Exposure and Risk Assessment

Exposure through drinking water is not of concern. Drinking water estimates were incorporated directly in the exposure model. For more information, please refer to the aggregate risk assessment (Section 3.5).

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal and inhalation).

As residential use of metsulfuron methyl is not permitted, aggregate exposure is from dietary and drinking water exposures only (see Section 3.3 and 3.4). Chronic aggregate (food and water) exposures were less than the respective reference doses. Therefore, aggregate exposure from all relevant sources is not considered a health concern.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties (Section 2.2), metsulfuron methyl is very soluble in water, is not likely to volatilize from moist soil or water surfaces under field conditions, and is not likely to bioaccumulate in organisms. Environmental fate data for metsulfuron methyl are summarized in Appendix X, Table 1. Metsulfuron methyl is stable to hydrolysis at neutral and alkaline pH. However, under acidic conditions some hydrolysis is expected, albeit at a very slow rate. Phototransformation of metsulfuron methyl in water and soil is limited. Overall, abiotic processes (hydrolysis and phototransformation) do not significantly contribute to the dissipation of metsulfuron methyl in the environment.

In the aquatic environment, metsulfuron methyl is moderately persistent to persistent under aerobic conditions depending on the type of water/sediment system. Under anaerobic conditions, metsulfuron methyl is moderately persistent. In the terrestrial environment, metsulfuron methyl is slightly persistent to persistent under aerobic conditions depending on the soil type. At cooler temperatures the dissipation of metsulfuron methyl is slow in all environmental media. The major transformation products are triazine amine, carbamoyl guanidine, sulfonamide, o-demethyl metsulfuron methyl and saccharin. Dissipation of metsulfuron methyl under anaerobic soil conditions is shown to be relatively slow with no evidence of mineralization or major transformation products being detected.

Metsulfuron methyl does not bind strongly to soil and sediment and partitions mainly to the aqueous phase. Laboratory studies on adsorption/desorption and soil column leaching indicate that metsulfuron methyl and its transformation products have a potential to be mobile in a variety of soils. Metsulfuron methyl and its transformation products met all criteria identifying them as having a high probability of leaching. In terrestrial field studies conducted in Canada and the U.S., varying degrees of leaching have been identified. The extent of metsulfuron methyl leaching is related to the time of application, amount of rainfall and soil characteristics. The potential for leaching is especially prominent in non-acidic soils because of increased solubility and decreased adsorption. Leaching in terrestrial field studies ranged from very little leaching beyond 22-cm soil depth to leaching up to 35 cm.

There was, however, no evidence to suggest that leaching had stopped at 35 cm as soil from a greater depth was not sampled. No information is available regarding the leaching potential of metsulfuron methyl transformation products under field conditions. Canadian water monitoring data show detection of metsulfuron methyl in surface water (Appendix VIII), but at present there are no monitoring data for groundwater.

4.2 Effects on Non-target Species

The environmental risk assessment determines the potential for adverse ecological effects in each environmental compartment by comparing the ratio of the estimated environmental exposure to the ecotoxicological effect. The estimated environmental exposure concentration (EEC) is the initial or cumulative concentration of pesticide in the various sources of food, water and soil to which the organism is exposed. EECs are calculated by different methods for each media (food, water or soil). If multiple applications of pesticide are used, cumulative EECs are determined by using the time taken to decline to 50% of the original application (DT_{50}) using the minimum time interval between applications for each environmental media.

The risk assessment is initially conducted using a screening-level scenario which assumes maximum exposure (EEC) and the most sensitive toxicological endpoint for the organism of interest. This assumes direct application or overspray to the environmental media (food, water, soil) to which the organism is exposed. This is the most conservative scenario and generally does not reflect the exposure to which an organism would be subject to when the pesticide is applied according to the label instructions. Risk to the environment is calculated as a risk quotient (RQ) which is the ratio between the environmental exposure and the toxicological endpoint for the organism (i.e. RQ = EEC/toxicological endpoint). The threshold or level of concern for potentially harmful effects to an organism is an RQ value of 1 where the exposure exactly equals the toxicological endpoint. RQ values greater than or equal to 1 are considered to equal or exceed the level of concern which may result in potentially harmful effects to the organism. RQ values less than 1 indicate negligible risk to the organism because they are below the threshold for harmful effects. In the latter case, no further assessment is carried out. If the RQ is greater than or equal to 1, the level of concern, then a refinement of the risk assessment is carried out to assess the level of concern using scenarios which are a better approximation of exposure or toxicological effects and less conservative. Refinements can include (i) exposure from the fraction of pesticide which drifts onto non-target habitats, instead of assuming 100% overspray, and (ii) exposure from the amount of pesticide predicted in runoff, instead of assuming direct overspray to water (i.e. 100% exposure). The refinements may also consider different toxicity endpoints or a percentile of a species sensitivity distribution rather than the most sensitive endpoint. They may also consider the results of a mesocosm study using several species rather than the toxicity from a single species. Further refinements to the risk assessment may consider the use of monitoring data collected in the field rather than EECs generated by a model.

4.2.1 Effects on Terrestrial Organisms

A risk assessment of metsulfuron methyl to terrestrial organisms was based upon an evaluation of toxicity data on metsulfuron methyl to earthworms (acute contact), bees (acute oral and contact), four species of predatory and/or parasitic invertebrates, two species of birds (acute oral, dietary, and chronic), three species of mammals (acute oral and chronic), and 11 species of terrestrial plants (seedlings emergence, vegetative vigour and berry production). A summary of terrestrial toxicity data for metsulfuron methyl are presented in Appendix X, Table 2. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with

metsulfuron methyl. For birds and mammals, the lowest toxicity endpoints (acute oral, dietary and reproduction) were used to extrapolate toxicity endpoints for birds and mammals of different sizes (20, 100 and 1000 g for birds and 15, 35 and 1000 g for mammals).

To address differences in species sensitivity, the acute oral LD_{50} and dietary LC_{50}, converted to daily dose, was further divided by a safety factor of 10. The screening level assessment used relevant food categories representing specific feeding guilds for each bird and mammal size class consisting of 100% of a particular dietary item (plants, grain/seeds, insects and fruit). Estimated dietary exposures (EDE) for each bird and mammal size were calculated based on EECs for each feeding preference group at each application rate and food ingestion rates. As no small birds in North America are known to eat a diet primarily of leafy plant material or grass, EDEs for small birds (20 and 100 g) based on a 100% diet of plants were not calculated.

Metsulfuron methyl demonstrated no adverse toxicological effects on terrestrial invertebrates, birds or mammals on an acute oral, dietary and reproductive basis. As metsulfuron methyl is a herbicide, adverse effects to non-target terrestrial plants are expected. Exposure of hawthorn (*Crataegus monogyna L.*) to metsulfuron methyl is shown to reduce mature berry production. In addition, plant emergence and vegetative vigour studies conducted with 10 plant species indicated that, although the seeds of most plant species emerged successfully, plants did not follow normal growth patterns. The effects are likely due to the ability of metsulfuron methyl to inhibit the plant enzyme acetolactate synthase, hence stopping cell division and plant growth by blocking branched chain amino acid biosynthesis. No toxicity studies conducted with metsulfuron methyl transformation products were available for review.

The screening level risk assessment indicated that exposure to metsulfuron methyl does not pose a risk to terrestrial invertebrates, mammals and birds. Appendix X, Tables 3 and 4 summarize the risk assessment from metsulfuron methyl to terrestrial organisms.

As would be expected, the herbicide metsulfuron methyl poses a risk to non-target terrestrial plants. The level of concern (LOC) was exceeded by 450 times at the lowest application rate (4.5 g a.i./ha). Less than 0.2% of the metsulfuron methyl application rate (4.5–90 g a.i./ha) is expected to negatively affect non-target terrestrial plants (EC_{25} divided by the application rate).

As a result, a refinement of the risk assessment was conducted taking into consideration the concentrations of metsulfuron methyl that could be present in terrestrial habitat directly adjacent to the application field through drift of spray. Spray drift data for a medium ASAE droplet size, as is generally used in ground boom applications of herbicides, indicate that the maximum amount of spray that will drift one metre down wind from the point of application during spraying is 6%. Using this percent drift, the off-site EECs for metsulfuron methyl were calculated. Based on this method of refinement, metsulfuron methyl poses a reduced risk to non-target terrestrial plants directly adjacent to the application field. Exceedance of the LOC was reduced to 27 times from 450 times for the lowest application rate. Buffer zones will be required to mitigate the risk of metsulfuron methyl to non-target terrestrial plants. Table 5 (Appendix X) summarizes the refined risk assessment from metsulfuron methyl to non-target terrestrial plants.

4.2.2 Effects on Aquatic Organisms

Risk to aquatic organisms, acute and chronic, is based on an evaluation of toxicity data on metsulfuron methyl for 19 freshwater species (two invertebrate, two fish, three algal and eleven vascular plant) and one estuarine/marine species (algae). Some toxicity data on the transformation products were also available. A summary of aquatic toxicity data for metsulfuron methyl and its transformation products are presented in Table 2 (Appendix X). For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with metsulfuron methyl. The endpoints were derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of 10 for fish and amphibians (based on surrogate data from fish studies).

Metsulfuron methyl and its transformation products are not toxic to freshwater invertebrates and fish on an acute basis. Chronic effects to freshwater fish and invertebrates are not expected. No chronic toxicity data were available for estuarine/marine species. As metsulfuron methyl is a herbicide, adverse effects to non-target aquatic plants are expected. Metsulfuron methyl affected cell density, biomass and growth rate of freshwater and marine/estuarine algae. Metsulfuron methyl significantly affected frond density and biomass of duckweed and growth rate, root density and surface leaf area of other aquatic vascular plants. The transformation products did not adversely affect algae or aquatic vascular plants at the maximum concentrations tested.

The risk assessment was conducted using data for the most sensitive freshwater organisms tested *Daphnia magna*, bluegill sunfish (*Lepomis macrochirus*) and rainbow trout (*Oncorhynchus mykiss*), diatom (*Navicula pelliculosa*) and aquatic plant (*Batrachium trichophyllum)* as well as marine/estuarine algae *(Skeletonema costatum)*.

The screening-level risk assessment indicated that metsulfuron methyl and its transformation products are not a risk to freshwater invertebrates, fish, amphibians (based on surrogate data from fish studies) and algae. However, a potential risk to vascular plants from metsulfuron methyl was identified. The screening level risk assessment for metsulfuron methyl and its transformation products to aquatic organisms is summarized in Appendix 10, Tables 6 and 7, respectively. Although surface water monitoring data are available for metsulfuron methyl (Appendix VIII), these data are limited and were not used in the aquatic risk assessment because of the following source of uncertainties: 1) sampling was conducted at broad time intervals and at times that may not have captured maximum concentrations resulting from runoff events in the watershed; 2) samples were collected in areas where metsulfuron methyl may not have been used. The refined risk assessment, based on model generated EECs, indicated that metsulfuron methyl in drift of spray and runoff exceed the level of concern (RQ > 1) for aquatic plants. Appendix X, Tables 8 and 9 summarize the refined risk to aquatic plants from metsulfuron methyl spray drift and runoff, respectively.

5.0 Value

5.1 Commercial Class Products

5.1.1 Commercial Class Alternatives to Metsulfuron methyl

All metsulfuron methyl uses are supported by the registrant. There are no risk concerns for any of the registered uses. Consequently, no alternatives to the use of metsulfuron methyl were considered.

5.2 Domestic Class Products

There are no Domestic Class products containing metsulfuron methyl registered in Canada.

5.3 Value of Metsulfuron Methyl

In Canada, the estimated average annual losses caused by weeds (in the early 1990s) were $283.9 million in wheat, $74.5 million in barley and $4.1 million in forage grass for seed. Although a relatively small quantity is used, metsulfuron methyl contributes to the reduction of the economic losses incurred by weeds.

The most common use of metsulfuron methyl is on established creeping red fescue. Currently, only a few postemergent broadleaf herbicides are registered for use on established creeping red fescue and, with the exception of metsulfuron methyl, are Group 4 herbicides (synthetic auxins).

Western snowberry, trembling aspen, and other undesirable brush/woody plants are problem weeds in pasture, rangeland and non-crop areas. They not only reduce forage grass yields but also compete with native grasses. The currently registered selective herbicides for use on these sites to control brush/woody plants are limited to Group 4 herbicides with the exception of metsulfuron methyl. Moreover, metsulfuron methyl provides better control of those woody plants than the Group 4 alternatives because it translocates into the crown.

Metsulfuron methyl residue in soil can persist for a long period. This provides residual weed control, but potentially limits recropping options.

Consideration has to be given to the development of herbicide resistance in weeds associated with the use of metsulfuron methyl. Due to the widespread and frequent use of acetolactate synthase inhibiting (Group 2) herbicides such as metsulfuron methyl; and lack of rotation with herbicides with other modes of action, more resistant weed biotypes have been documented in Canada with Group 2 herbicides than with any other herbicide group, including 12 broadleaf weeds (cleavers, chickweed, hemp-nettle, kochia, lamb's-quarters, giant ragweed, ball mustard, wild mustard, redroot pigweed, Russian thistle, spiny annual sowthistle, and stinkweed) and two grassy weeds (green foxtail and wild oats). The use of good crop and herbicide rotations, recommended sanitation practices and other integrated management techniques should help ensure that metsulfuron methyl will continue to be an effective weed control tool.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, metsulfuron methyl was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of metsulfuron methyl were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use products. The PMRA has reached the following conclusions:

- The *n*-octanol–water partition coefficient (log K_{ow}) of metsulfuron methyl is 0.0018, which is below the TSMP Track 1 cut-off criterion for log $K_{ow} \geq 5.0$. Metsulfuron methyl meets the criteria for persistence in water as its half-life values in water (277 days), are above the TSMP Track 1 cut-off criteria for water (≥182 days). However metsulfuron methyl does not meet the criteria for persistence in soil; the half-life determined for metsulfuron methyl in soil (10–178 days) is below the TSMP Track 1 cut-off for sediment (≥182 days) and soil (≥182 days). The vapour pressure and Henry's law constant indicate that metsulfuron methyl will not volatilize from water or moist soil under field conditions, thus long-range atmospheric transport of metsulfuron methyl is not likely to occur.

Therefore, the use of metsulfuron methyl is not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Human Health and Safety

7.1.1 Occupational Risk

The occupational application and postapplication risks are acceptable for the exposure scenarios involving the use of metsulfuron methyl. The calculated margins of exposure for application and postapplication occupational exposures are all above the Agency's target assuming that workers wear baseline personal protective equipment.

7.1.2 Dietary Risk from Food and Water

The aggregate dietary (food and water) risk assessments demonstrate that there were no dietary concerns for any population subgroup in Canada, including infant, children teenagers, adults and senior. In addition, no dietary concerns were evident for nursing or pregnant females or based on gender in general.

7.1.3 Dietary Risk from Drinking Water

The potential for the contamination of drinking water with metsulfuron methyl is expected to be negligible. There are no drinking water concerns for any population subgroup in Canada, including infant, children teenagers, adults and senior.

7.1.4 Residential Risk

Metsulfuron methyl is not registered for use in any residential areas so a residential risk assessment was not required.

7.2 Environmental Risk

Metsulfuron methyl is slightly to moderately persistent in most soils and moderately persistent to persistent in water systems. There is a potential that under appropriate environmental conditions metsulfuron methyl may through runoff appear in surface water. The risk assessment of metsulfuron methyl indicates that adverse effects on non-target terrestrial and aquatic plants are expected. Therefore, additional risk-reduction measures are required.

7.3 Value

From the value perspective, metsulfuron methyl is acceptable for continued registration.

8.0 Proposed Regulatory Decision

The PMRA is proposing that metsulfuron methyl is acceptable for continued registration with the implementation of the proposed risk-reduction measures. These measures are required to further protect human health and environment. As a condition of the continued registration of metsulfuron methyl uses, new risk-reduction measures must be included on the labels of all products. No additional data are being requested at this time.

8.1 Proposed Regulatory Action Related to Human Health

The PMRA has determined that the dietary and drinking water risks, worker risks during mixing, loading and application are acceptable for all uses provided that the mitigation measures listed in Appendix XI are implemented.

8.1.1 Residue Definition for Risk Assessment and Enforcement

Division 15, Table II, of the Food and Drug Regulations currently identifies metsulfuron methyl methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbony]amino]sulfonyl]benzoate, including the metabolite methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl] amino]sulfonyl] 4-hydroxybenzoate as the residue for risk assessment and enforcement.

Based on barley and wheat metabolism studies, the proposed residue definition for plant commodities is metsulfuron methyl and its metabolite 4-hydroxy metsulfuron methyl (hydroxylated metabolite) and methyl glucose metsulfuron methyl (glucosed metabolite).

Based on animal metabolism studies the proposed residue definition is metsulfuron methyl.

8.1.2 Maximum Residue Limits for Metsulfuron methyl in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian maximum residue limits and to remove MRLs that are no longer supported.

As indicated in Table 8.1.2 the Food and Drug Regulations specify MRLs for metsulfuron methyl residues in animal commodities. Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specified MRL must not exceed the general MRL of 0.1 ppm.

Where no specific MRL for a pest control product has been established in the Food and Drug Regulations, subsection B.15.002(1) applies. This requires that residues do not exceed 0.1 ppm and has been considered a general MRL for enforcement purposes. Currently, residues of metsulfuron methyl in all agricultural commodities, including those approved for treatment in Canada are regulated by subsection B.15.002(1). However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*.

Evaluation of the available residue data for barley and wheat indicate that residues would not exceed the general MRL provided the conditions of use as specified on the product labels are followed. If and when the general MRL is revoked, a transition strategy will be established to allow permanent MRLs to be set for barley and wheat grain.

Table 8.1.2 Proposed Metsulfuron methyl MRLs for Commodities Approved for Treatment in Canada

Common Chemical Name	Chemical Name of Substance	Maximum Residue Limit (ppm)	Foods
Metsulfuron methyl	methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbony]amino]sulfonyl]benzoate	0.5	Kidney of cattle, goat and hog
		0.1	Fat, meat and meat by-product of cattle, goat and hog
		0.05	Milk

For supplemental MRL information regarding the International situation and trade implications, refer to Appendix XII.

8.2 Proposed Regulatory Action Related to Environment

To reduce the effects of metsulfuron methyl in the environment, mitigation in the form of precautionary label statements and buffer zones are required. Environmental mitigation statements are listed in Appendix XI.

8.3 Proposed Regulatory Action Related to Value

Amendments to the labels arising from the re-evaluation of this active ingredient are proposed in Appendix XI.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
AHAS	acetohydroxyacid synthase
ALS	acetolactate synthase
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
atm	atmospheres
bw	body weight
CFIA	Canadian Food Inspection Agency
cm	centimetre(s)
d	day(s)
DEEM®	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time to 50% (the dose required to observe a 50% decline in the test population)
DWLOC	drinking water level of comparison
EC_{25}	exposure concentration to 25% (a concentration causing 25% adverse effects in the test population
EC_{50}	exposure concentration to 50% (a concentration causing 50% adverse effects in the test population
EChE	erythrocyte cholinesterase
EDE	estimated daily exposure
EEC	expected environmental concentration
EPA	Environmental Protection Agency (US)
EXAMS	Exposure Analysis Modeling System
F_0	parental animals
F_1	first filial generation
g	gram(s)
GAP	good agricultural practice
GC-FPD	Gas Chromatography-Flame Photometric Detector
GC-MSD	Gas Chromatography-Mass Selective detector
GC-NPD	Gas Chromatography-Nitrogen Phosphorous Detector
h	hour(s)
ha	hectare(s)
Hg	mercury
IRED	Interim Reregistration Eligibility Decision (USEPA Document)
K_d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)

LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population
LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
LOAEL	lowest observed adverse effect level
LOC	Level of Concern
LOD	limit of detection
LOEC	lowest observed effect concentration
m	metre(s)
m/sec	metre(s) per second
m^3	metre(s) cubed
mg	milligram(s)
mg	microgram(s)
mL	millilitre(s)
mm	millimetre(s)
MOE	margin of exposure
nd	no detection
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OC	organic carbon
OM	organic matter
PChE	plasma cholinesterase
PCP	Pest Control Product
PDP	Pesticide Data Program (United States data)
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PRZM	Pesticide Root Zone Model
PSI	pre-slaughter interval
Q_1^*	cancer potency factor
REI	restricted-entry interval
RQ	risk quotient
TC	transfer coefficient
TGAI	technical grade active ingredient
TP	transformation product
TPM	triophanate-methyl
TSMP	Toxic Substances Management Policy
URMULE	User Requested Minor Use Label Expansion
USEPA	United States Environmental Protection Agency
wk	week
yr	year
°C	degree(s) Celsius

Appendix I Registered metsulfuron methyl products as of 9 August 2006

Registration Number	Marketing Class[1]	Registrant	Product Name	Formulation Type	Guarantee (%)
20213	T	E.I. du Pont Canada Company	Metsulfuron Methyl Technical Herbicide	Solid	97.7
20214	C		Ally Herbicide Dry Flowable 60%	Wettable granules	60
23005	C		Dupont Escort Herbicide 60% Dry Flowable		
24388	C		Ally Herbicide Toss-N-Go 60% Dry		
25578	C		Metsulfuron Methyl EUP Toss-N-Go		
25579	C		Metsulfuron Methyl EUP Herbicide		
26677	M		Metsulfuron Methyl MUP Herbicide		

[1] T = Technical grade active ingredient; M = Manufacturing concentrate; C = Commercial.

NOTE: Discontinued products or products with a submission for discontinuation are not included.

Appendix II Registered uses of metsulfuron methyl as of 9 August 2006[1]

Use Site Category	Sites		Weeds[2]	Maximum Application Rate (g a.i./ha)	Use Supported?[3]
13, 14 Terrestrial feed crops and terrestrial food crops	Wheat (spring and durum)	Prairie provinces and Peace River Region of BC (Soil pH 7.9 or lower)	A	4.5	Y
	Barley				
13 Terrestrial feed crops	Established creeping red fescue				
	Established creeping red fescue, orchard grass, crested and intermediate wheat grass for feed or seed production		A plus narrow-leaved hawksbeard		M
	Pasture and rangeland	Prairie provinces and BC	Western snowberry	15	Y
			Wild rose	18	
		BC	Field scabious and perennial pepperweed	39068	M
13, 16 Terrestrial feed crops and Industrial and domestic vegetation control for non-food sites	Rough turf and non-crop areas	Prairie provinces and BC	B	12	Y
			B plus western snowberry	15	
			C	18	
		BC	Field scabious and perennial pepperweed	38703	M
	Rangeland and non-crop area (utility rights of way, roadsides, industrial sites, fencelines)	Prairie provinces and BC	Balsam poplar and willow	60	Y
			Cherry and trembling aspen	90	

[1] The formulation type for all supported end-use products is wettable granules. Application is made once per year by ground equipment only. No aerial application is allowed for any uses. Information on application equipment and the number of applications is based on both label use information and information provided by the registrant under DACO 5.2. Uses of tank mix products including the pre-packaged tank mixes are not presented.

[2] A = Ball mustard, blue bur, Canada thistle*, chickweed, common groundsel, corn spurry, cow cockle, flixweed, green smartweed, hemp-nettle, kochia, lady's-thumb, lamb's-quarters*, prostrate pigweed, redroot pigweed, Russian thistle*, scentless chamomile, shepherd's-purse, sow thistle (annual; perennial)*, stinkweed, stork's-bill, tartary buckwheat, toad flax*, volunteer rapeseed**, wild buckwheat*, wild mustard

B = Common tansy, kochia, Russian thistle, scentless chamomile, sweet clover, Canada thistle*, sow thistle*, dandelion*

C = Common tansy, kochia, Russian thistle, scentless chamomile, sweet clover, Canada thistle*, sow thistle*, dandelion, and western snowberry

[3] Y = Use is currently registered and supported by the registrant

M = Use was added as a User Requested Minor Use Label Expansion and is supported by the registrant.

* Suppression only

** Metsulfuron methyl alone will not control imazethapyr-tolerant canola varieties.

Appendix III Toxicology Profile for Metsulfuron Methyl

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species/ # of Animals per Group	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies		
Metabolism of ^{14}C-phenyl-labelled metsulfuron methyl—CD rats		Absorption: rapid absorption (based on the rate of excretion) Distribution: Within 72 hours only 0.27–3.91% of the original dose remained in organs and tissues. After the hide, the carcass and the GI tract, the liver contained the highest percent of radioactivity—up to 0.014% of the dose—with all other tissues and organs containing less. (The hide, which contained up to 3.56% of the dose in low dose males and 0.944% in high dose females, was likely contaminated by excrement in the cage). Tissue residues were, therefore, minimal. For the low dose < 0.03 ppm; high dose females had higher levels ranging frm 0.8 ppm in brain to 7.1 ppm in liver and 8.0 ppm in kidneys, than did males (0.1 ppm in blood to 1.6 ppm in liver and 2.6 ppm in kidneys). Metabolism: Four metabolites and parent were recovered in both urine and feces in all treatment groups. Parent compound accounted for most of the urinary and fecal activity (77-90% and 1.8–6.2% of the administered dose, respectively). Total metabolites, urine + feces, accounted for app. 5.4–8.2% of the dose. The four metabolites were: (1) Metabolite I: (methyl 2-[(amino)sulfonyl] benzoate) (2) Metabolite II: (2-[(amino) sulfonyl]-benzoic acid) (3) Metabolite III: (methyl 2-[[[(amino) carbonyl] amino] sulfonyl] benzoate) (4) Saccharin The major metabolic pathway was a breakdown of the urea bridge to give rise to either Metabolite I or Metabolite III and the triazine amine derivative. The secondary biotransformation was demethylation of Metabolite I to form Metabolite II and Saccharin. Excretion: Within 72 hours (96 hr for high dose) 71 -95% of the administered dose was recovered in the urine, and 5-13% in the feces [At 24 hr: low dose urine: 69-78%, feces: 2.1-7.3%; preconditioned dose urine: 85 - 90%, feces 2.4-3.7%; high dose urine 34-53%, feces 4.1-6.1%]
Metabolism of ^{14}C triazine-labelled metsulfuron methyl—CD rats		Absorption: rapid absorption [based on the rate of excretion (which is similar to that of the above study at the comparable high dose)] Distribution: 0.2-0.6% in the carcass or tissues 96 hr post-dosing -highest conc. was in G.I. tract and skin (0.08% and 0.007% of dose) Metabolism:-in urine over 96% of urine radioactivity co-chromatographed with metsulfuron methyl in 3/4 rats (84% in 1/4) and most of the remaining co-chromatographed with triazine amine with one small unidentified area (0.5-1.6%). The triazine portion was produced by cleavage of the sulfonylurea bridge. - in feces 74-91% of radioactivity co-chromatographed with metsulfuron methyl, 1.9-14.4% with o-demethyl triazine amine, 1.8-6.2% with hydroxymethyl metsulfuron methyl, 1.2-2.9% with triazine amine, 2.2-9.1% with either of two unidentified areas Excretion:- 83-86% of the original dose excreted in the urine, 3-6% in the feces, and none in expired CO_2, 96 hr post-dosing - in 3/4 rats over half the dose was excreted within 24 hr. and a mean of 95% was excreted within 72 hr.

Study/Species/ # of Animals per Group	NOAEL (mg/kg bw/day)	Results/Effects
Acute Toxicity Studies		
Acute oral toxicity—mouse	LD_{50} > 5000 mg/kg bw Signs: slight ↓bw (1♀ at 7 days) LOW TOXICITY	
Acute oral toxicity—rat	LD_{50} > 5000 mg/kg bw Signs: stained and wet perineal areas, ↓bw (♀) Necropsy: a few dark red foci scattered through out the lungs (1♂), enlarged liver (1♀) LOW TOXICITY	
Acute dermal toxicity—rabbit	LD_{50} > 2000 mg/kg bw Signs: intermittent weight loss LOW TOXICITY	
Acute inhalation toxicity—rat	LC_{50} > 5.3 mg/L Signs: ↓bw, slight brown nasal discharge (day following exposure) LOW TOXICITY	
Eye irritation—rabbit	Moderate area of slight corneal clouding,, moderate iritic injection, severe to moderate conjunctivitis [Note: this study used 2 animals only. A later study, using 6 animals and higher dosages, showed much less irritation (minimally irritating), however it is necessary to default to the most severe response] SEVERELY IRRITATING	
Dermal irritation—rabbit	NON-IRRITATING	
Dermal sensitization - Guinea pig	NON-SENSITIZER	
Subchronic Toxicity Studies		
21-day dermal —rabbit	dermal/systemic:125	dermal: ≥500 mg/kg bw/day: diffuse/multifocal dermatitis 2000 mg/kg bw/day: slight to severe erythema, slight to moderate edema systemic: ≥500 mg/kg bw/day: ↑diarrhea
90-day oral (feeding) —mouse	≥666	no adverse effects at the highest dose tested
90-day oral (feeding) —rat	≥521/84(♂/♀)	521/659 mg/kg bw/day: ↓bw (♀ - 5-9% less at wks 2-6, 8, and 10-13), ↓bw gains (♀ - 12% less overall)
90-day oral (feeding) —Beagle dog	≥125	no adverse effects at the highest dose tested
Chronic Toxicity/Oncogenicity Studies		
18-month feeding study —mouse	≥666	There were no significant treatment -related effects Study may not have reached MTD, but is close enough to limit dose in ♀ at 836 mg/kg bw/day to be acceptable. Not carcinogenic

Study/Species/ # of Animals per Group	NOAEL (mg/kg bw/day)	Results/Effects
Two-year feeding study—rat	25	250 mg/kg bw/day: ↓bw (♂ - 7.4% - 13 wks, 5.8% - 52 wks, 9.1% - 104 wks; ♀ - 6.5% - 13 wks, 7.4% - 52 wks, but not at 104 wks), ↓bw gains (12.2%/14.4% (♂/♀) - wks 0-13; 8.4%/13.1% (♂/♀) - wks 0-52), slight ↓food consumption (1st 8 wks; ♀ continued during 1st six months), ↑organ/bw [52 wks - kidney(♂), brain, heart]. There was a possible dose-related increase in liver neoplastic nodules in males but the increase did not exceed historical controls [♂/♀ - 0/1, 0/1, 2/0, 3/0, 4/2 at 0, 0.25, 1.25, 25, 250 mg/kg bw/day; incidence in males was 6.1% at 250 mg/kg bw/day which is within the historical control range of 3-14% (mean 6.6%)]. There was also an increased incidence of C-cell adenomas of the thyroid in females (0 mg/kg bw/day: 2.9%; 250 mg/kg bw/day 10.9%). The incidence at 250 mg/kg bw/day (10.9%) is within the historical control range of 0-14% (mean 4.0%). Only animals that died between week 52-104 (all groups) and control and high dose animals sacrificed terminally were examined. Not carcinogenic
Reproductive and Developmental Toxicity Studies		
Two-generation reproduction feeding study— rat	Parental: 34 Offspring/Reproductive: ≥342	Parental:342-474 mg/kg bw/day:↓bw [F_0 (13 wks pre-mating 10.4%/8.8% - ♂/♀) and F_{1b} (13 wks pre-mating 6.5%/6.7% - ♂/♀)]; ↓bw gain [F_0 (0-13 wks pre-mating 14.4%/16.6% - ♂/♀) and F_{1b} (0-13 wks pre-mating 6.7%/1.0% - ♂/♀)]. Offspring/Reproductive: 342-474 mg/kg bw/day: ↓mean live litter size (F_{2a} -25%). This is probably not related to treatment since statistically significant effects did not occur in F_1 and F_{2b} litter groups.
Developmental study (gavage)— rat	Maternal: 40 Developmental: ≥1000	Maternal: ≥250 mg/kg bw/day: clinical signs (vocalization to touch, ungroomed coat, excess salivation, "tip-toe" walking), ↑bw gain post-treatment period (9%), ↑food consumption post-treatment period (9%) [slight reductions in bw gain during treatment were not significant; no reduction in food consumption during treatment]. 1000 mg/kg bw/day: clinical signs (urine-stained abdominal fur), ↓bw (GD 14 - 4%), ↓bw gain during treatment period (24%)(↑bw gain post-treatment period - 10%), ↑food consumption post-treatment period (6%). Developmental: no treatment-related effects No evidence of teratogenicity
Developmental study (gavage)—rabbit	Maternal: 100 Developmental: ≥700	Maternal: 300 mg/kg bw/day: treatment-related deaths (2 - GD 19 and 26), stomach wall pitted (1), abortions (2) ↓bw gain (GD6-9 - minus 0.11 kg vs plus 0.02 kg), "anorexia" and red or orange-coloured urine, decreased motor activity and impaired righting reflex. 700 mg/kg bw/day: treatment-related deaths (12 - GDs 14-24), stomach wall thin (4) or with red/black petechiae (2), abortions (1), ↓bw gain (GD6-9 - minus 0.17 kg vs plus 0.02 kg; GD6-18 - minus 0.26 kg vs plus 0.04 kg), "anorexia" and red or orange-coloured urine, decreased motor activity and impaired righting reflex, hair in stomach. Developmental: no treatment-related effects No evidence of teratogenicity

Study/Species/ # of Animals per Group	NOAEL (mg/kg bw/day)	Results/Effects
Genotoxicity Studies		
Ames reverse mutation test —*Salmonella typhimurium* TA1535, TA1537, TA98, TA100	Negative	
In vivo micronucleus test - CD-1 mouse	Negative	
In vivo cytogenetics assay - rat bone marrow	Negative	
In vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells	Positive - clastogenic with and without activation inducing significant increases in structural chromosome aberrations	
In vitro gene mutation assay—CHO/HGPRT cells	Negative	
In vitro unscheduled DNA synthesis assay—rat primary hepatocytes (3×)	Negative	

Appendix IV Toxicology Endpoints for Health Risk Assessment for Metsulfuron Methyl

Exposure Scenario	Dose (mg/kg bw/day)	Endpoint	Study	UF/SF or MOE[a]
Acute dietary	An acute reference dose was not calculated since there was not an endpoint of concern			
Chronic dietary	NOAEL = 25	Decreased body weight, body weight gain and food consumption, increased relative kidney, brain and heart weights	2-year feeding study—rat	300 An additional 3× safety factor was added to provide a margin of safety of at least 1000 to the NOAEL (100 mg/kg bw/day) for maternal death noted in the rabbit developmental study. Since the chronic rat NOAEL of 25 mg/kg bw/day is partially protective for the maternal death, a full 10x for severity of effect is not required.
	ADI = 0.0833 mg/kg bw/day			
Short[b]-, and intermediate[c]-term dermal General Population	NOAEL = 125	Increased diarrhea	21-day dermal study—rabbit	100
Short[b]-, and intermediate[c]-term dermal Females 13+	NOAEL = 100	Increased mortality, decreased body weight gain, decreased motor activity, impaired righting reflex, and orange/red-coloured urine	Developmental study—rabbit	1000 extra factor of 10 for severity of effect
Short[b]-, and intermediate[c]-term inhalation[d] General Population	NOAEL = 84	Decreased body weight and body weight gain, decreased serum protein	90-day feeding study—rat	100

Exposure Scenario	Dose (mg/kg bw/day)	Endpoint	Study	UF/SF or MOE[a]
Short[b]-, and intermediate[c]-term inhalation[d] Females 13+	NOAEL = 100	Increased mortality, decreased body weight gain, decreased motor activity, impaired righting reflex, and orange/red-coloured urine	Developmental study—rabbit	1000 extra factor of 10 for severity of effect
Cancer	non-carcinogenic			

a UF/SF refers to total of uncertainty and/or safety factors for dietary assessments, MOE refers to desired margin of exposure for occupational or residential assessments.

b Duration of exposure is 1-30 days.

c Duration of exposure is 1-6 months.

d Because an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

Appendix V Summary of Occupational Risk Estimates for Metsulfuron Methyl

Table 1 Route Specific MOEs for Mixers/Loaders/Applicators of Products Containing Metsulfuron Methyl

Baseline PPE: long-sleeved shirt, long pants and chemical-resistant gloves (open cab, no gloves for groundboom application)									
Crop	**Method of Application**	**Formulation[a]**	**Application Rate[b]**	**Area Treated per day[c]**	**Daily Exposure (µg/kg/day)**		**Margins of Exposure[f] Target = 1000**		
					Dermal	**Inhalation no respirator**	**Dermal[d]**	**Inhalation[e] no respirator**	**Combined[g] no respirator**
Barley, wheat (spring and durum), forage grasses[h]	Groundboom	WG	0.0045 kg a.i./L	Farmer: 100 ha	0.443	0.013	230 000	7 900 000	220 000
				Custom: 300 ha	1.328	0.038	75 000	2 600 000	73 000
		WG in WSP		Farmer: 100 ha	0.111	0.007	900 000	15 000 000	850 000
				Custom: 300 ha	0.333	0.02	300 000	4 900 000	280 000
Pasture and rangeland	Groundboom	WG	0.018 kg a.i./L	Farmer: 100 ha	1.771	0.051	56 000	2 000 000	55 000
				Custom: 300 ha	5.312	0.153	19 000	650 000	18 000
		WG in WSP		Farmer: 100 ha	0.444	0.027	230 000	3 700 000	210 000
				Custom: 300 ha	1.333	0.082	75 000	1 200 000	71 000
Rough turf and non-crop land	Backpack	WG	0.00018 kg a.i./L	150 L	0.757	0.025	130 000	4 100 000	130 000
		WG in WSP			0.735	0.024	140 000	4 200 000	130 000
	Low pressure handwand	WG			2.666	0.549	38 000	180 000	31 000
		WG in WSP			0.127	0.017	790 000	5 700 000	690 000
	High pressure handwand	WG	0.000018 kg a.i./L	3 750 L	1.94	0.147	52 000	680 000	48 000
		WG in WSP			1.885	0.146	53 000	690 000	49 000
	Right-of-way sprayer	WG			0.343	0.006	290 000	17 000 000	290 000
		WG in WSP			0.293	0.005	340 000	20 000 000	340 000

Baseline PPE: long-sleeved shirt, long pants and chemical-resistant gloves (open cab, no gloves for groundboom application)									
Crop	**Method of Application**	**Formulation[a]**	**Application Rate[b]**	**Area Treated per day[c]**	**Daily Exposure (µg/kg/day)**		**Margins of Exposure[f] Target = 1000**		
					Dermal	**Inhalation no respirator**	**Dermal[d]**	**Inhalation[e] no respirator**	**Combined[g] no respirator**
Non-crop areas and rangeland[i]	Backpack	WG	0.0009 kg a.i./L	150 L	3.786	0.123	26 000	810 000	26 000
		WG in WSP			3.676	0.12	27 000	830 000	26 000
	Low pressure handwand	WG			13.328	2.744	7 500	36 000	6 200
		WG in WSP			0.637	0.087	160 000	1 100 000	140 000
	High pressure handwand	WG	0.00009 kg a.i./L	3 750 L	9.702	0.733	10 000	140 000	9 600
		WG in WSP			9.426	0.728	11 000	140 000	9 800
	Right-of-way sprayer	WG			1.715	0.029	58 000	3 400 000	57 000
		WG in WSP			1.466	0.025	68 000	4 000 000	67 000

[a] Formulations are defined as followed: WG = wettable granules (open mixing/loading); WG in WSP = wettable granules in water-soluble packaging (closed mixing/loading)

[b] Maximum label rate.

[c] Default tier 1 area treated per day values.

[d] Dermal MOE = dermal NOAEL / dermal exposure. The short- and intermediate-term dermal NOAEL is 100 mg/kg bw/day. Dermal exposure = (dermal unit exposure value × area treated per day × use rate × DA) / BW . (DA = dermal absorption of 100%; BW = body weight of 70 kg)

[e] Inhalation MOE = inhalation NOAEL / inhalation exposure. The short- and intermediate-term inhalation NOAEL is 100 mg/kg bw/day. Inhalation exposure = (Inhalation unit exposure value × area treated per day × use rate)/ BW. (BW = body weight of 70 kg)

[f] Target MOE of 1000 for short- and intermediate-term exposure scenarios.

[g] Combined MOE = $\frac{1}{(1/MOE_{Dermal}) + (1/MOE_{Inhalation})}$

[h] Forage grasses = creeping red fescue, orchard grass, crested and intermediate wheatgrass.

[i] Non-crop land = roadsides, utility rights-of-way, industrial sites, fencelines.

Table 2 Postapplication Exposure Estimates for Re-entry into Fields Treated with Metsulfuron Methyl

Crop and Rate (kg a.i./ha)	Number of Applications per year	Activity	Transfer Coefficient [a] (cm^2/hour)	Peak DFR [b] (µg/cm^2) (at day 0)	Systemic Exposure [c] (µg/kg bw/day)	MOE [d] (Target = 1000)	Proposed REI [e] (hours)
USC 13 and 14: Terrestrial Feed and Food Crops							
Barley, wheat (spring and durum) and forage grasses (creeping red fescue, orchard grass, crested and intermediate wheatgrass) Rate: 0.0045	1	Scouting (min. foliage)	100	0.009	0.036	2 800 000	12
		Scouting, irrigation (full foliage)	1500	0.009	0.54	190 000	12
Pasture and rangeland Rate: 0.018	1	Scouting (min. foliage)	500	0.036	0.72	140 000	12
		Scouting (full foliage)	1500	0.036	2.16	46 000	12
USC 16: Industrial and Domestic Vegetation Control for Non-Food Sites							
Rough turf and non-crop land Rate: 0.018	1	Scouting, mechanical weeding and mowing (min. foliage)	500	0.036	0.72	140 000	12
		Scouting, mechanical weeding and mowing (full foliage)	1500	0.036	2.16	46 000	12
Non-crop areas and rangeland Rate: 0.09	1	Scouting, mechanical weeding and mowing (min. foliage)	500	0.18	3.6	28 000	12
		Scouting, mechanical weeding and mowing (full foliage)	1500	0.18	10.8	9 300	12

[a] Transfer coefficients are from the Science Advisory Council for Exposure, Policy No. 003.1 (U.S. EPA, 2000) and any amendments thereof.

[b] DFR calculations are based on a default peak residue value of 20% of the application rate and 10% dissipation rate per day. Based on one application per season.

[c] Systemic exposure = DFR × TC x 8 hrs × DA /70 kg. (TC = transfer coefficient; DA = dermal absorption of 100%)

[d] Based on worker short-term NOAEL of 100 mg/kg bw/day and target MOE of 1000. MOE = NOAEL/Exposure

[e] REI = Restricted-entry interval

Appendix VI Dietary Exposure and Risk Estimates for Metsulfuron methyl

Metsulfuron methyl		
Chronic exposure ADI = 0.0833 mg/kg bw/day		
Population	**Exposure**	**%ADI**
Canadian Population (total)	0.000833	1
All infants (<1 year)	0.000998	1.2
Children 1–2 yrs	0.00292	3.5
Children 3–5 yrs	0.002236	2.7
Children 6–12 yrs	0.001428	1.7
Youth 13–19 yrs	0.00078	0.9
Adults 20–49 yrs	0.000594	0.7
Adults 50+ yrs	0.000508	0.6
Females 13–49 yrs	0.000558	0.7

Appendix VII Residue Chemistry Summary for Metsulfuron methyl

1.1 Metabolism

The PMRA concluded that the residue chemistry database for metsulfuron methyl is largely complete. Nature and magnitude of the residue in plants and livestock are adequately understood. Conclusions from the United States Environmental Protection Agency are consistent with the PMRA's conclusions.

1.1.1 Plant Metabolism

The PMRA has reviewed plant metabolism studies conducted on barley and wheat grains in order to determine the degradation pathway of metsulfuron methyl as well as the nature and magnitude of residues using radiolabelled. The PMRA has concluded that the qualitative nature of the residues of metsulfuron methyl is adequately understood. Hydroxylation of the phenyl ring followed by carbohydrate conjugation was the major metabolic pathway of metsulfuron methyl in barley and wheat, with its glucose metabolite as the major degradate. As well, metsulfuron methyl may undergo hydrolysis or cleavage of the sulfonylurea bridge, resulting in the formation of metabolites at much smaller amounts than its glucose metabolite. This may result in triazine amine and sulfonamide derivatives evolving to saccharin through cyclization. In all cereal grain studies, the percentages of metabolites of the total radioactive residues increase as the percentage of parent compound declines.

1.1.2 Livestock Metabolism

The PMRA has reviewed livestock metabolism studies conducted on cattle and goat in order to determine the degradation pathway of metsulfuron methyl as well as the nature and magnitude of residues. As well, conclusion from EPA and scientific literature on hens have been reviewed. The PMRA has concluded that undegraded metsulfuron methyl is rapidly eliminated as the major radiolabelled component and that the major route of elimination is via urinary excretion. Minimum transfer residue (less than 0.01ppm) of metsulfuron methyl has been observed in milk (0.009 ppm) and tissues; as well, minimum transfer residue has been reported in eggs and tissues of hens. The PMRA concluded that there was no evidence of accumulation of metsulfuron methyl or its metabolites in any organ or tissue.

Metabolism of metsulfuron methyl in animals appears to follow two main degradation pathways, either hydrolysis to the corresponding sulfonamide or cleavage of the heterocyclic ring. The major pathway, breakdown of the urea bridge, leads to either aminosulfonyl benzoate or sulfonamide and the triazine amine derivative. The secondary biotransformation pathway was demethylation of aminosulfonyl benzoate to form saccharin.

1.1.3 Residue Definition

Based on cereal grain metabolism studies and given the similarity in metabolic profile, the residues of concern were defined as metsulfuron methyl and its hydroxylated and glucose conjugates in plants. As the procedure used in analytical method is based on the determination of both its metabolites reported as hydrolxylated metabolite, the proposed residue definition is metsulfuron methyl and its hydroxylated metabolite.

Based on goat and cattle metabolism studies, the similarity in metabolic profile and the fact that no metabolites occur at detectable levels (< 0.01 mg/kg) in cereal grain, even at exaggerated rates of application, the residue of concern was defined as metsulfuron methyl *per se* in animals.

1.2 Analytical Methods

1.2.1 Methods for Residue Analysis of Plants and Plant Products

The PMRA has reviewed analytical methodology capable of determining residues of metsulfuron methyl and its metabolites in cereal grains. An HPLC method is used to determine residues of metsulfuron methyl in the grain, straw and green forage samples. Residues were analysed by normal phase liquid chromatography using a photoconductivity detector. The limit of quantitation for grain and green forage was 0.02 ppm and 0.05 ppm for straw.

EPA has assessed a HPLC/UV method (Morse Laboratories SOP#METH-82, revision 2) to determine residues of metsulfuron methyl in/on grain sorghum. The validated limit of quantitation for residues of metsulfuron *per se* is 0.1 ppm in/on grain and stover and 0.05 ppm in/on forage. The LOQ for the combined residues of hydroxylated and glucosylated conjugates is 0.1 ppm in/on grain and stover and 0.05 ppm in/on forage.

1.2.2 Methods for Residue Analysis of Food of Animal Origin

The PMRA has reviewed analytical methodologies capable of determining residues of metsulfuron methyl in bovine cream, fat, feces, milk, tissues and urine. An HPLC method is used to determine residues of metsulfuron methyl in bovine samples. Residues were analysed by normal phase liquid chromatography using a photoconductivity detector. Recoveries from fortified samples ranged from from a low 54-85% for subcutaneous fat to a high of 73-138% for kidney.

1.2.3 Multiresidue Analytical Methods

The multiresidue method for fruits and vegetables of the CFIA does not list metsulfuron methyl as one of the pesticides that has been evaluated through the MRM protocols. As well, none of the U.S. Food and Drug Administration multi-residue protocols (A to E) is applicable for the analysis of metsulfuron methyl. Multiresidue methods are not suitable for the analysis of metsulfuron methyl.

1.3 Food Residues

1.3.1 Storage Stability

Storage stability describing the magnitude of residues in pasture and range grass after treatment with metsulfuron methyl has been reviewed. No appreciable degradation of metsulfuron methyl or its hydroxylated or glucosylated metabolites were detected in wheat green forage after 33 months (for MEM) and after 18 months for its metabolites.

1.3.2 Crop Residues

The PMRA has reviewed residue data for oat, barley and wheat. These crops were treated at rates up to 8 times the recommended rate and the samples were collected at PHIs of 75-91 days. The residues in all crops were less than 0.02 ppm (LOQ of the analytical method) and the residues in wheat straw were found to be less than 0.05 ppm (LOQ of the analytical method).
Also, EPA stated that the results of an analyses of sorghum grain, fodder and stover (at seed maturity), forage and hay (30 days), after application of metsulfuron methyl at the maximum proposed label rate and twice the rate, show that all residues of metsulfuron methyl and its hydroxylated and glucosylated metabolites were below the limit of quantitation (0.05 or 0.1 ppm).

1.3.3 Livestock Residues

The PMRA has reviewed the fate on metsulfuron methyl ingested by dairy cows. Residues in all tissue types of all animals, regardless of dose rate, were lower than 0.01 ppm when animal slaughter occurred 1 week post-treatment. Total radioactive residues were mainly observed in kidney. Additionally, there appears to be no concern for this compound's ability to bioaccumulate in lipophilic tissue. A K_{ow} of 0.018 indicates a low potential for bioaccumulation in fatty tissues.

1.3.4 Confined Accumulation in Rotational Crops

The PMRA has reviewed crop rotation trials conducted in filed and under greenhouse conditions. Under field trial conditions, confined crop rotation was conducted on oat, rape, soybean and sorghum at an application rate of 30 g a.i./ha and a one-year plantback interval. Residues of parent compound or its metabolites were not detected in any edible crop commodities. Under greenhouse conditions, confined crop rotation was conducted on oat, rape, soybean and sugarbeet at an application rate of 70 g a.i./ha and a 120-day plantback interval. Residues of parent compound or its metabolites were not detected in any edible crop commodities.

Results from these studies indicated that metsulfuron methyl occured at an extremely small percentage of the radioactivity in the crop samples, suggesting that the use of metsulfuron methyl should not expose consumers to detectable residues in food. Results of these studies indicated that ^{14}C residues detected in soybean foliage at maturity (greenhouse conditions) and in rape seed (field conditions) exceeded 10 ppb. Further investigations were conducted showing that actual level of metsulfuron methyl were less than 0.3 ppb in these commodities.

Rotation options are determined by soil pH, the crop to be planted and a minimum interval. Interval prior to planting (months after application) ranged from 10 months for spring wheat to 48 months for canary seed and yellow mustard. Land previously treated with metsulfuron methyl can not be rotated to crops other than those listed until a field bioassay confirms that residues are not present.

Appendix VIII Water Monitoring Data

A search for metsulfuron methyl water monitoring data in Canada revealed that routine analysis for metsulfuron methyl is not conducted. Provincial and territorial departments responsible for water quality monitoring were contacted for a summary of existing water monitoring data for the sulfonyl-ureas that are currently under re-evaluation. In addition, requests for existing data were submitted to Environment Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada. Recently Environment Canada began analysing for sulfonyl ureas in 2003–2005. Metsulfuron methyl was not detected in Saskatchewan drinking water reservoirs, whereas, it was detected in two drinking water reservoirs in Alberta and three drinking water reservoirs in Manitoba at maximum concentrations of 0.12 and 2.10 ng/L, respectively. Of 10 rivers and creeks monitored in the prairie provinces, metsulfuron methyl was detected in only one creek in Saskatchewan at a maximum concentration of 1.58 ng/L. Two dugouts that were known drinking water sources were sampled and one of these dugouts had metsulfuron methyl detections at a detection frequency of 96% and maximum concentration of 1.66 ng/L. Metsulfuron methyl was detected in 2 of 6 wetlands in 10 and 40% of samples, respectively. The highest surface water concentration was reported in an Albertan wetland at 77.79 ng/L.

The concentrations of mobile pesticides in surface water are directly related to the frequency and timing of monitoring in relation to pesticide application and runoff events. Therefore, timing and frequency of sampling is likely to be the most important factor influencing the concentration detected and the frequency of detections. A review of the available water monitoring data revealed that details on the application of metsulfuron methyl were not available. For instance, the application rate applied, when the application occurred and weather conditions prior to sampling were not known or reported. Without this information, it is difficult to conclude if non-detects were a result of non-transport or more simply a result samples being collected from areas where metsulfuron methyl is not used. In addition, sampling was conducted at broad intervals (i.e. weekly, monthly) that may not have captured maximum concentrations resulting from runoff events in the watershed.

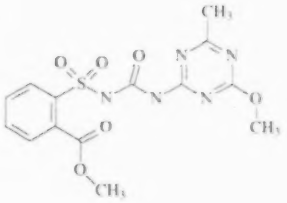
Given the scarcity of data available in Canada for residues of metsulfuron methyl in water, U.S. databases were searched for detections of metsulfuron methyl. Data on metsulfuron methyl residues in potential drinking water sources in the U.S. was reviewed from 2 sources available in published open literature. Metsulfuron methyl was detected in only 1 of 207 groundwater samples and 2 of 24 surface water samples collected in Florida at a concentration of 2.3 and 8.1 µg/L respectively. In the second study, in 212 water samples collected from 75 surface water and 25 groundwater sites located in Midwestern states, metsulfuron methyl was not detected. The detection limits of the analytical methods used in the U.S. studies (10–1000 ng/L), may not have been sensitive enough to detect metsulfuron methyl in the water samples that were collected.

In view of the uncertainty caused by the above factors, the limited water monitoring data, that were available, were not used in the environmental risk assessment.

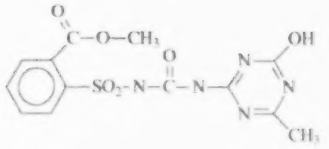
Appendix IX Major transformation products of metsulfuron methyl

(Dupont chemical code numbers are shown in parentheses)

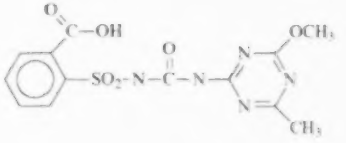
Metsulfuron methyl
Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2yl)
-amino]carbonyl]amino]sulfonyl]benzoate



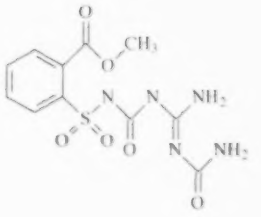
O-demethyl metsulfuron methyl (IN-B5067)
Methyl 2-[[[[(4-hydroxy-6-methyl-1,3,5-triazin-2yl)
amino]carbonyl]amino]sulfonyl]benzoate



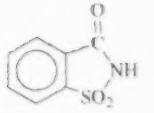
(IN-F5438)
2-(4-methoxy-6-methyl- 1,3,5-triazin-2-yl)
amino]carbonyl]amino]sulfonyl]benzoic acid



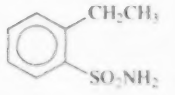
(IN-NC148)
Carbamoyl Guanidine



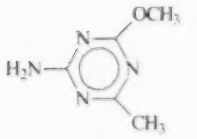
Saccharin (IN-581)
1,2-benzisothiazol-3(2H)-one,1,1-dioxide



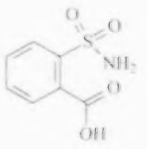
Sulfonamide (IN-D5803)
Methyl 2-(aminosulfonyl)benzoate



Triazine amine (IN-A4098)
4-Methoxy-6-methyl-1,3,5-triazin-2-amine



(IN-D5119)
Benzoic Acid, 2-(Aminosulfonyl)



Appendix X Environmental Fate and Toxicity

Table 1 Environmental Fate of Metsulfuron methyl and its transformation products

Study type	Test material	Study Conditions	Value or Endpoint	Interpretation	Major transformation products
Abiotic transformation					
Hydrolysis	Metsulfuron methyl	30 d	15°C 25°C pH 5 100.4 d 22.1 d pH 7 Stable pH 9 Stable	Not a major route of transformation at low temperature and at neutral and basic conditions	Saccharin and sulfonamide formed under acidic conditions
Phototransformation soil	Metsulfuron methyl	Silt loam	pH 4.3 , >30 d pH 6.4, 99 d	Not a major route of transformation	Saccharin
Phototransformation water	Metsulfuron methyl	25°C, 35 d	Not determined. No difference in rates of transformation between irradiated test solutions and dark controls.	Not a major route of transformation	Major transformation products were not formed (i.e. > 10% of applied a.r.)
Biotransformation					
Soil - aerobic	Metsulfuron methyl	12 months; 20°C; pH 5.2; % OM 1.8	Half-life: 10–11 d	Non persistent	Carbomoyl guanidine, sulfonamide, O-demethyl metsulfuron methyl, triazine amine
		27 months; 25°C; pH 9.0; % OM 2.6	Half-life: 111.2 d	Moderately persistent	Not determined.
		24 weeks, pH 6.4; % OM 2.75; temperature not reported	Half-life: 27.3 d	Slightly persistent	No major transformation products were detected > 10% of applied a.r.
		3 soils: 14 weeks; pH 5.6–6.7; % OM 1.4–4.02	Half-life: 16.8–23.8 d	Slightly persistent	Saccharin, sulfonamide
		3 soils: 84–98 d; 20°C; pH 5.2–7.5; % OM not reported	Half-life: 70–178 d	Moderately persistent to persistent	No major transformation products were detected > 10% of applied a.r.
		7 soils: 105 d; 25°C; pH 5.6–7.8; % OM 2.3–19	Half-life: 24–44 d	Slightly persistent to moderately persistent	Not determined.
	Triazine amine	3 soils: 123 d; 20°C; pH 5.7–7.7; % OM 1.2–2.6	Half-life: 22–76 d	Slightly to moderately persistent	Not determined.

Study type	Test material	Study Conditions	Value or Endpoint	Interpretation	Major transformation products
	O-demethyl metsulfuron methyl	3 soils: 121 d;20°C, pH 5.7–7.7; % OM 1.2–2.6	Half-life: 27–33 d	slightly persistent	Not determined
Soil - anaerobic	Metsulfuron methyl	120 d;20°C; pH 5.1; % OM 1.5	Stable	Persistent	No major transformation products were detected > 10% of applied a.r.
Water/sediment - aerobic	Metsulfuron methyl	Two systems: 119 d; 20°C; pH 7.6–9	Half-life: 43–239 d water; 47–277 d whole system	Moderately persistent to persistent. No significant accumulation in the sediment	metsulfuron, triazine amine
		Two systems: 91 d; 20°C; pH 7.3–7.6	Half-life: 133–294 d whole system	Moderately persistent to persistent. No significant accumulation in the sediment	metsulfuron
Water/sediment-anaerobic	Metsulfuron methyl	365 d; 25°C; pH 5.6–6.6	Half-life: 49–76 d whole system	Moderately persistent	saccharin, 2-(aminosulfonyl) benzoic acid
Mobility					
Adsorption/ desorption	Metsulfuron methyl	Four soils: 25°C; pH 5.6–6.5; % OM 0.3–4.02	K_d 0.36–1.4 K_{oc} 60–212	Very high to high mobility	Not determined
	Metsulfuron methyl	Eight soils: 25°C; pH 5.3–7.7; % OM 2.3–19	K_d 0.04–4.6 K_{oc} 3–41	Very high mobility	Not determined
	Triazine amine	Three soils: 20°C; pH 5.9–7.5; % OM 1.3–2.6	K_d 0.15–0.7 K_{oc} 6–30	High to very high mobility	Not determined
	O-demethyl metsulfuron methyl	Three soils: 20°C; pH 5.7–7.7; % OM 1.2–2.6	K_d 0.24–0.43 K_{oc} 13–20	High to very high mobility	Not determined
Soil column leaching	Metsulfuron methyl	Four soils (pH 5.6–6.7; non-aged and aged (30 days)	% recovered in leachate as metsulfuron methyl non-aged: 87–106% % recovered in leachate as metsulfuron methyl aged: 54–76%		Saccharin
Soil thin layer chromatography	Metsulfuron methyl	Four soils: Soil characteristics not reported.	Rf = 0.65–1.0	Mobile to highly mobile	Not reported

Study type	Test material	Study Conditions	Value or Endpoint	Interpretation	Major transformation products
Field studies					
Field dissipation	Metsulfuron methyl	Seven U.S. sites: Delaware, North Carolina, Florida, Mississippi, Colorado, Ohio, North Dakota Three Canadian sites: Alberta, Saskatchewan, Manitoba pH range: 4.3–8.2	Half-life: 1 week to 7 months Evidence that leaching may have occurred beyond 35 cm depth in some soils.		Saccharin

Table 2 Environmental toxicity of metsulfuron methyl and its transformation products

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
Terrestrial Species						
Invertebrate	Acute oral	Honey bee (*Apis mellifera*)	Technical	48-h LD_{50}	> 43 µg a.i./bee	mortality
	Acute contact	Earthworm (*Eisenia foetida*)	Technical	14-d LC_{50}	> 1000 mg a.i./kg soil	mortality
		Honey bee (*Apis mellifera*)	Technical	48-h LD_{50}	> 25 µg a.i./bee	mortality
		Predatory mite (*Typhlodromus pyri*)	Formulation (20% purity)	14-d beneficial capacity	-1.2%	% effect on survival and reproduction combined
		Parasitic wasp (*Aphidius rhopalosiphi*)		15-h beneficial capacity	19.3%	
		Green lacewing (*Chrysoperla carnea*)	Formulation (60% purity)	8-wk beneficial capacity	-9.9%	

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
		Carabid beetle (*Poecilus cupreus*)	Formulation (20% purity)	15-d beneficial capacity	0%; 3.3% reduction	mortality; prey consumption
Birds	Acute oral	Mallard duck (*Anas platyrhynchos*)	Technical	LD_{50}	>2510 mg a.i./kg bw	mortality
	Dietary	Bobwhite quail (*Colinus virginianus*)		LD_{50}	5620 mg a.i./kg diet	mortality
		Mallard duck (*Anas platyrhynchos*)		LD_{50}	5620 mg a.i./kg diet	mortality
	Reproduction	Bobwhite quail (*Colinus virginianus*)		NOEC	>1020 mg a.i./kg diet	reproduction
		Mallard duck (*Anas platyrhynchos*)		NOEC	>1000 mg a.i./kg diet	reproduction
Mammals	Acute	Rat	Technical	LD_{50}	>5000 mg a.i./kg bw	mortality
	Chronic	Mouse	Technical	18 month NOEC	5000 mg a.i./kg bw	mortality
	Reproduction (2-generation)	Rat	Technical	Parental/ Reproductive NOEC	500 mg a.i./kg diet	reproduction
				Offspring NOEC	5000 mg a.i./kg diet	reproduction
Plants	Seedling emergence	11 plant species	Formulation (60% purity)	EC_{25}, NOEC	0.19–1.02 g a.i./ha 0.16 – 2.63 g a.i./ha	height emergence
	Vegetative vigour			EC_{25}, NOEC	0.07–17.09 g a.i./ha 0.04–6.23 g a.i./ha	Shoot dry weight
				EC_{25}, NOEC	0.07–23.96 g a.i./ha 0.03–6.23 g a.i./ha	Height

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
	berry production (hawthorn hedge, *Crataegus monogyna)*		Metsulfuron methyl 4 g a.i./ha	EC_{25}	0.01 g a.i./ha	reduced mature berry production
Freshwater Organisms						
Invertebrates	Acute	*Daphnia magna*	Technical	48-h LC_{50}, NOEC	>120–>720 mg a.i./L 120 - 420 mg a.i./L	immobility
				48-h LC_{50}, NOEC	>720 mg a.i./L 420 mg a.i./L	
			Triazine amine	48-h LC_{50}, NOEC	>99 mg a.i./L 25 mg a.i./L	
		Crayfish	Technical	96-h LC_{50}, NOEC	>178 mg a.i./L 178 mg a.i./L	mortality
	Chronic	*Daphnia magna*	Technical	21-d LC_{50}, NOEC	>100 mg a.i./L 100 mg a.i./L	Decreased adult growth, number of offspring per adult
			Triazine amine	21-d NOEC	>97 mg a.i./L	
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	Technical	96-h LC_{50}, NOEC	>113–>150 mg a.i./L 100–113 mg a.i./L	mortality
			Triazine amine	96-h LC_{50}, NOEC	>0.93 mg a.i./L 0.93 mg a.i./L	mortality
		Bluegill sunfish (*Lepomis macrochirus*)	Technical	96-h LC_{50}, NOEC	>119–>150 mg a.i./L 119–150 mg a.i./L	mortality
			Formulation (21% purity)	96-h LC_{50}, NOEC	>210 mg a.i./L 139 mg a.i./L	mortality
	Chronic (Early Life Stage)	Rainbow trout (*Oncorhynchus mykiss*)	Technical	NOEC	4.5 mg a.i./L	Decreased fry survival and growth

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
Algae	Acute	Green algae (*Selenastrum capricornutum*)	Technical	72-h EC_{50} NOEC	157–875 µg a.i./L 58.5 µg a.i./L	Cell density, biomass and growth rate
			Formulation (% ai not reported)	72-h EC_{50} NOEC	359–1307 µg a.i./L 125 µg a.i./L	
			Triazine amine	72-h EC_{50} NOEC	>10 µg a.i./L 10 µg a.i./L	
			metsulfuron	72-h EC_{50} NOEC	>11 µg a.i./L 11 µg a.i./L	
		Blue-green algae (*Anabaena flos-aquae*)	Technical	120-h EC_{50} NOEC	> 95 µg a.i./L 95 µg a.i./L	
		Diatom (*Navicula pelliculosa*)		120-h EC_{50} NOEC	>94 µg a.i./L 94 µg a.i./L	
Vascular* Plants	Acute	10 plant species	Technical	7-d EC_{50} 14-d EC_{50} 21-d EC_{50} 7-d EC_{50} 14-d EC_{50} 21-d EC_{50}	1.08 (0.12) µg a.i./L 0.8 (0.15)–10.44 (2.96) µg a.i./L 1.13 (0.28) µg a.i./L 0.75 (0.46)–0.83 (0.16) µg a.i./L 0.07 (0.04)–6.62 (0.17) µg a.i./L 0.10 (0.09)–0.79 (0.56) µg a.i./L	relative growth rate surface leaf area
		Common water milfoil (*Myriophyllum sibiricum*)	Technical	14-d EC_{50}	0.22 µg a.i./L	Decreased dry root mass
		Duck weed (*Lemna gibba*)	Technical	14-d EC_{50} NOEC	0.36 µg a.i./L 0.16 µg a.i./L	Chlorosis of fronds
			triazine amine	14-d EC_{50} NOEC	> 11.5 µg a.i./L 11.5 µg a.i./L	frond number and biomass

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
			Methyl 2-[[[[(4-hydroxy-6-methyl-1,3,5-triazine-2yl) amino]carbonyl]amino]sulfonyl]benzoate		>0.40–0.66 µg a.i./L 0.24 µg a.i./L	
			Metsulfuron	14-d EC_{50}	>10.3 µg a.i./L	
Marine/Estuarine organisms						
Algae	Acute	*Skeletonema costatum*	Technical	120-h EC_{50} NOEC	>93.6 µg a.i./L 93.6 µg a.i./L	

* Endpoint standard deviations shown in parentheses

Table 3 Summary of screening level risk assessment of metsulfuron methyl to terrestrial invertebrates and plants

Organism	Exposure	Endpoint reported	Use Rate (g a.i./ha)	EEC	RQ*
Invertebrates					
Honeybee	Acute contact	LD_{50} > 25 µg a.i./bee (28 kg a.i./ha)	90	9.0×10^{-2} kg a.i./ha	3.2×10^{-3}
Earthworm		LD_{50} > 1000 mg a.i./kg soil	90	4.0×10^{-2} kg a.i./ha	4.0×10^{-5}
Plants					
Plants	Berry production (hawthorn hedge, *Crataegus monogyna*)	EC_{25} = 0.01 g a.i./ha	4.5	4.5 g a.i./ha	**450**

* Risk quotients (RQ) shown in bold exceed the level of concern (RQ > 1)

Table 4 Summary of screening level risk assessment of metsulfuron methyl to birds and mammals

Organism	Exposure	Endpoint* (mg a.i./kg body weight/day)	Food guild	EDE (mg a.i./kg body weight/day)	RQ**
Birds					
Small (20 g)	Acute Oral	251	insectivore	4.5	$1.7 \cdot 10^{-2}$
			granivore	0.8	$3.0 \cdot 10^{-3}$
			fructivore	2.3	$9.0 \cdot 10^{-3}$
	Dietary	31.8	insectivore	4.5	$1.4 \cdot 10^{-1}$
			granivore	0.8	$2.5 \cdot 10^{-2}$
			fructivore	2.3	$7.2 \cdot 10^{-2}$
	Reproduction	56.6	insectivore	4.5	$8.0 \cdot 10^{-2}$
			granivore	0.8	$1.4 \cdot 10^{-2}$
			fructivore	2.3	$4.1 \cdot 10^{-2}$
Medium (100 g)	Acute Oral	251	insectivore	3.5	$1.4 \cdot 10^{-2}$
			granivore	0.6	$2.0 \cdot 10^{-3}$
			fructivore	1.8	$7.0 \cdot 10^{-3}$
	Dietary	31.8	insectivore	3.5	$1.1 \cdot 10^{-1}$
			granivore	0.6	$1.9 \cdot 10^{-2}$
			fructivore	1.8	$5.7 \cdot 10^{-2}$
	Reproduction	56.6	insectivore	3.5	$6.2 \cdot 10^{-2}$
			granivore	0.6	$1.1 \cdot 10^{-2}$
			fructivore	1.8	$3.2 \cdot 10^{-2}$

Organism	Exposure	Endpoint* (mg a.i./kg body weight/day)	Food guild	EDE (mg a.i./kg body weight/day)	RQ**
Large (1000 g)	Acute	251	insectivore	1	4.0×10^{-3}
			granivore	0.2	8.0×10^{-4}
			fructivore	0.5	2.0×10^{-3}
			herbivore	6.4	2.5×10^{-2}
	Dietary	31.8	insectivore	1	4.0×10^{-3}
			granivore	0.2	8.0×10^{-4}
			fructivore	0.5	2.0×10^{-3}
			herbivore	6.4	2.0×10^{-1}
	Reproduction	56.6	insectivore	1	1.8×10^{-2}
			granivore	0.2	4.0×10^{-3}
			fructivore	0.5	9.0×10^{-3}
			herbivore	6.4	2.0×10^{-1}
Mammals					
Small (15g)	Acute Oral	500	insectivore	2.6	5.0×10^{-3}
			granivore	0.4	1.0×10^{-3}
			fructivore	1.3	3.0×10^{-3}
			herbivore	16.3	3.3×10^{-2}
	Reproduction	34	insectivore	0.4	7.0×10^{-3}
			granivore	1.3	1.2×10^{-2}
			fructivore	16.3	3.8×10^{-2}
			herbivore	16.3	4.8×10^{-1}

Organism	Exposure	Endpoint* (mg a.i./kg body weight/day)	Food guild	EDE (mg a.i./kg body weight/day)	RQ**
Medium (35g)	Acute Oral	500	insectivore	2.3	5.0×10^{-3}
			granivore	0.4	1.0×10^{-3}
			fructivore	1.2	2.0×10^{-3}
			herbivore	14.3	2.9×10^{-2}
	Reproduction	34	insectivore	2.3	6.8×10^{-2}
			granivore	0.4	1.2×10^{-2}
			fructivore	1.2	3.5×10^{-2}
			herbivore	14.3	4.2×10^{-1}
Large (1000 g)	Acute Oral	500	insectivore	1.2	2.0×10^{-3}
			granivore	0.2	4.0×10^{-4}
			fructivore	0.6	1.0×10^{-3}
			herbivore	7.6	1.5×10^{-2}
	Reproduction	34	insectivore	1.2	3.5×10^{-2}
			granivore	0.2	6.0×10^{-3}
			fructivore	0.6	1.8×10^{-2}
			herbivore	7.6	2.2×10^{-1}

* Acute oral and dietary endpoints that were originally expressed as a concentration (mg a.i./kg diet) have been converted to daily dose (mg a.i./kg body weight/day) and further divided by a factor of 10 in order to address differences in species sensitivity.

** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 5 Refined risk assessment of metsulfuron methyl to terrestrial plants

Organism	Exposure	EC_{25} (g a.i./ha)	Use Rate (g a.i./ha)	% application rate to reach EC_{25}	Drift EEC* (g a.i./ha)	RQ**
Plants	Berry production (hawthorn hedge, *Crataegus monogyna*)	0.01	4.5	0.22	0.27	**27**
			12	0.08	0.72	**72**
			15	0.07	0.9	**90**
			18	0.06	1.08	**108**
			60	0.02	3.6	**360**
			90	0.01	5.4	**540**

* Based on drift of 6% for a default droplet size of medium (herbicides).

** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 6 Summary of screening level risk assessment of metsulfuron methyl to aquatic organisms

Organism	Exposure	Species	Endpoint reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	Use Rate (g a.i./ha)	EEC** (mg a.i./L)	RQ***
Freshwater Species							
Invertebrate	Acute	*D. magna*	LC_{50} > 115	57.5	90	0.011	1.9×10^{-4}
	Chronic	*D. magna*	NOEC = 100	100	90	0.011	1.1×10^{-4}
Fish	Acute	Rainbow trout	LC_{50}>113	11.3	90	0.011	9.7×10^{-4}
	Chronic	Bluegill sunfish (Early Life Cycle)	NOEC > 79.4	7.9	90	0.011	1.4×10^{-3}
Plant	Acute	Diatom	120-h EC_{50} = 0.0939	0.00939	90	0.011	2.3×10^{-3}
	Acute	*Batrachium trichophyllum*	EC_{50} = 0.00007	0.000035	4.5	0.00056	$\mathbf{1.6 \times 10^{1}}$

Organism	Exposure	Species	Endpoint reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	Use Rate (g a.i./ha)	EEC** (mg a.i./L)	RQ***
Amphibian	Acute	Rainbow trout (surrogate)	LC_{50} >113	11.3	90	0.06	5.3×10^{-3}
	Chronic	Fish Early Life Cycle (surrogate)	NOEC > 79.4	7.9	90	0.06	7.6×10^{-3}
Estuarine and Marine Species							
Plant	Acute	Algae	EC_{50} = 0.0936	0.0468	90	0.011	2.4×10^{-1}

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

** EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms.

*** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 7 Summary of screening level risk assessment of metsulfuron methyl transformation products to aquatic organisms

Organism	Exposure	Species	Endpoint reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	Use Rate (g a.i./ha)	EEC** (mg a.i./L)	RQ***
Triazine amine							
Invertebrate	Acute	*D. magna*	LC_{50} > 99	49.5	90	0.004	8.1×10^{-5}
	Chronic		21-d NOEC = 100	100			4.0×10^{-5}
Fish	Acute	Rainbow trout	LC_{50} > 0.93	0.093	90	0.004	4.3×10^{-2}
Algae	Acute	Green algae	72-h EC_{50} > 10	5	90	0.004	8.0×10^{-4}
Plants	Acute	Duckweed	EC_{50} > 11.5	5.5	90	0.004	7.3×10^{-4}
Amphibian	Acute	Rainbow trout (surrogate)	LC_{50} > 0.93	0.093	90	0.033	3.5×10^{-1}

O-demethyl metsulfuron methyl							
Plants	Acute	Duckweed	$EC_{50} > 0.4$	0.2	90	0.011	5.5×10^{-2}
IN-F5438							
Plants	Acute	Duckweed	$EC_{50} > 10.3$	5.15	90	0.011	2.1×10^{-3}

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

** EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms. EECs for transformation products were determined by assuming 100% conversion of metsulfuron methyl to the transformation products and correcting for molecular weight.

*** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 8 Refined risk assessment of metsulfuron methyl for freshwater organisms from spray drift

Organism	Exposure	$EC_{50} \div 2$* (µg a.i./L)	Use Rate (g a.i./ha)	Drift EEC** (µg a.i./L)	RQ***
Plants	Acute	0.035	4.5	0.04	**1.1**
			12	0.09	**2.6**
			15	0.11	**3.1**
			18	0.14	**4**
			60	0.45	**12.9**
			90	0.68	**19.4**

* Endpoints used in the acute exposure risk assessment for aquatic plants are derived by dividing the EC_{50} from the appropriate laboratory study by a factor of two (2).

** Based on drift of 6% for a default droplet size of medium (herbicides).

*** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 9 Refined risk assessment of metsulfuron methyl for freshwater organisms from predicted run-off

Endpoint (µg a.i./L)	Use Rate (g a.i./ha)	EEC (µg a.i./L)*	RQ**
Vascular plants			
0.035	4.5	0.21	**6**
	18	0.8	**22.9**

* 90th percentile of 21d average runoff values. This time frame was chosen because it most closely matches the 14 day exposure time used to generate the endpoint for the most sensitive aquatic plant, *Batrachium trichophyllum*. The models that were used to predict EECs resulting from runoff are based on an agricultural scenario consisting of a 1 ha wetland with an average depth of 0.8 m and a 10 ha drainage area. EECs were not predicted for the highest application rates (60 and 90 g a.i./ha) that are used on utility rights of way, fencelines, roadsides and industrial sites as these areas constitute a low percentage of area in the Prairie provinces and British Columbia.

** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Appendix XI Label Amendments for Commercial Class Products Containing Metsulfuron methyl

Canadian commercial end-use product labels must be amended to include the following statements to further protect workers and the environment.

FOR ALL FORMULATIONS:

Add to **DIRECTIONS FOR USE:**

- Do not re-enter treated fields until 12 hours after application.
- Apply only when the potential for drift to areas of human habitation or areas of human activity (houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature, application equipment and sprayer settings.

Field sprayer application:

- DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty.
- DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification.

- For application to rights-of-way, buffer zones for protection of sensitive terrestrial habitats are not required; however, the best available application strategies which minimize off-site drift, including meteorological conditions (e.g. wind direction, low wind speed) and spray equipment (e.g. coarse droplet sizes, minimizing height above canopy), should be used. Applicators must, however, observe the specified buffer zones for protection of sensitive aquatic habitats.

  Buffer zones:
  The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrub lands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Application rate (and use)*	Buffer Zones (metres) Required for the Protection of:		
	Freshwater Habitat of Depths:		Terrestrial habitat
	0.8 m	> 1 m	
4.5 g a.i./ha (crops)	1	0	15
12 g a.i./ha (pasture and rangeland)	1	1	30
15 g a.i./ha (pasture and rangeland)	1	1	35
18 g a.i./ha (pasture and rangeland)	2	1	40
60 g a.i./ha (non-crop areas)	4	2	120
90 g a.i./ha (non-crop areas)	5	3	120

* For field sprayer application, buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy or ground, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy or ground, the labelled buffer zone can be reduced by 30%.

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

Use of the following spray methods or equipment DO NOT require a buffer zone: hand-held or backpack sprayer, inter-row hooded sprayer, spot treatment, soil drench, and soil incorporation.

Add to **PRECAUTIONS:**

- Mixers, loaders and applicators must wear long-sleeved shirt, long pants, and chemical-resistant gloves (gloves not required for groundboom sprayers).

Add to **ENVIRONMENTAL HAZARDS:**

- TOXIC to aquatic organisms and non target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Runoff:
To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to: heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g. soils that are compacted or fine textured such as clay).

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Leaching:
The use of this chemical may result in contamination of groundwater, particularly in areas where soils are permeable (e.g. sandy soil) and/or the depth to the water table is shallow.

Add to **DISPOSAL**:

Disposal statements should be in compliance with the PMRA Directive, DIR99-04, *Disposal Statements for Control Product Labels*.

FOR WETTABLE GRANULE FORMULATIONS:

Add to **DIRECTIONS FOR USE:**

- Drop intact water-soluble package (WSP) directly into spray tank. The WSP and pesticide will dissolve readily in water.
- Do not allow the WSP to become wet prior to use. Do not handle individual WSP with wet hands or wet gloves as this may cause breakage. Do not remove WSP from over-wrap container except for immediate use.
- Do not open water-soluble bags or attempt to remove the contents from them. The contents are not designed to be re-measured or subdivided.
- Do not use opened or punctured WSP.
- If broken WSP is found when the over-wrap bag is opened, avoid contact with, and inhalation of the product. Handle with chemical-resistant gloves and dispose of broken WSP according to the DISPOSAL section.

FOR FORMULATION PCP Reg. No. 25578 and 25579:
On the primary panel, the statement which reads "..... ALSO, FOR CONTROL OF UNDESIRABLE BRUSH/WOODY PLANT SPECIES IN PASTURE, RANGELAND, AND NON-CROP AREAS IN THE PRAIRIE PROVINCES." must be revised to read "..... ALSO, FOR CONTROL OF UNDESIRABLE BRUSH/WOODY PLANT SPECIES IN RANGELAND AND NON-CROP AREAS IN THE PRAIRIE PROVINCES." to delete the unspecified use on pasture.

FOR FORMULATION PCP Reg. No. 23005, 25578 and 25579:
Under the heading "DIRECTIONS FOR USE", the sub-heading "ROUGH TURF AND NON-CROP AREAS" must be changed to read "ROUGH TURF AND NON-CROP AREAS such as Utility Rights of Way, roadsides, industrial sites, fence lines" to achieve a consistent description of non-crop areas

Appendix XII Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Metsulfuron methyl residues resulting from Canadian label uses on animal food commodities are covered by B.15.002(1) of the Food and Drug Regulations, while general regulation B.15.002(1) applies to all foods where a specific MRL has not been established. However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

As noted in Section 8.1.1 Residue Definition for Risk Assessment and Enforcement and Section 8.1.2 Maximum Residue Limits for metsulfuron methyl in Food, the PMRA proposes to modify the residue definition for both enforcement and risk assessment purposes.

Table 1 Comparison between MRLs in Canada and in Other Jurisdictions for Metsulfuron methyl

Commodity	MRL or Tolerance (ppm)		
	Canada	United States[2]	Codex
Kidney of cattle, goat and hog	0.5	0.5	None
Fat, meat and meat byproduct of cattle, goat and hog	0.1	0.1	None
Milk	0.05	0.05	None
Barley grain	0.11	0.1	None
Sugarcane	0.11	0.05	None
Wheat grain	0.11		None

Notes

1 Where no MRL is specified residues are regulated to not exceed 0.1 ppm by virtue of the Food and Drugs Regulations, B.15.002(1).

2 As per Title 40 Part 180.428 of the United States Code of Federal Regulations.
See also www.access.gpo.gov/nara/cfr/waisidx_01/40cfr180_01.html

Table 2 Residue Definition in Canada and Other Jurisdictions

Jurisdiction	Residue definition	
	Plant	**Animal**
Canada	methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbony]amino]sulfonyl]benzoate, including the metabolite methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl] 4-hydroxybenzoate	
US	(methyl 2-[[[[(4-methoxy-6- methyl-1,3,5-triazin-2-yl)amino] carbonyl]amino]sulfonyl]benzoate) and its metabolite methyl 2-[[[[(4- methoxy-6-methyl-1-,3,5-triazin-2-yl)amino]carbonyl]amino] sulfonyl]-4-hydroxybenzoate	methyl-2[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl] amino]sulfonyl]benzoate)
Codex	None	None